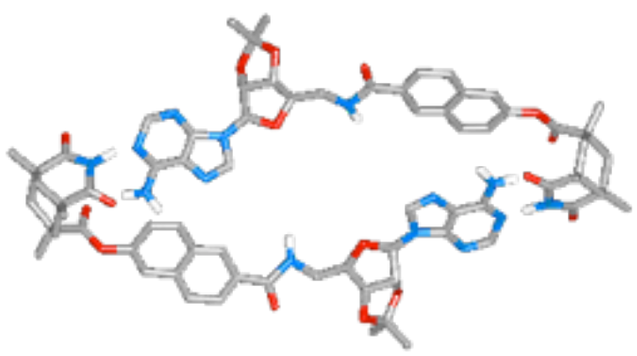
Autocatalysis and Self-Replication

~ toward synthesis of *THE LIFE* ~



Lit. Seminar
2011.1.8 (Sat)
Katsuya Sato (B4)

Outline of Topics

I. Introduction
~ Concept of Autocatalysis ~

II. Asymmetric Autocatalysis
~ Soai Reaction ~

III. Organic Autocatalysis
~ Synthetic Autocatalyst ~

IV. Biological Autocatalysis
~ Self-Replication of RNA ~

V. Summary

Today's Keywords

asymmetric amplification / autocatalysis / homochirality /non-linear effect / ribozyme / RNA world / self-replication / Soai reaction /

Today's Key-persons

K. Soai

J. Rebek, Jr.

G. F. Joyce

Recent Reports

K. Soai *Science* **2009**, *324*, 492-495
J. Rebek, Jr *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 541-544
G. F. Joyce *Science* **2009**, *323*, 1229-1232

I. Introduction

~ Concept of Autocatalysis ~

- ✤ What is Autocatalysis?
- ✤ Examples
- ✤ Scientific Importance

Definition

***Autocatalysis* is...**

catalysis of a chemical reaction by one of the products of the reaction.

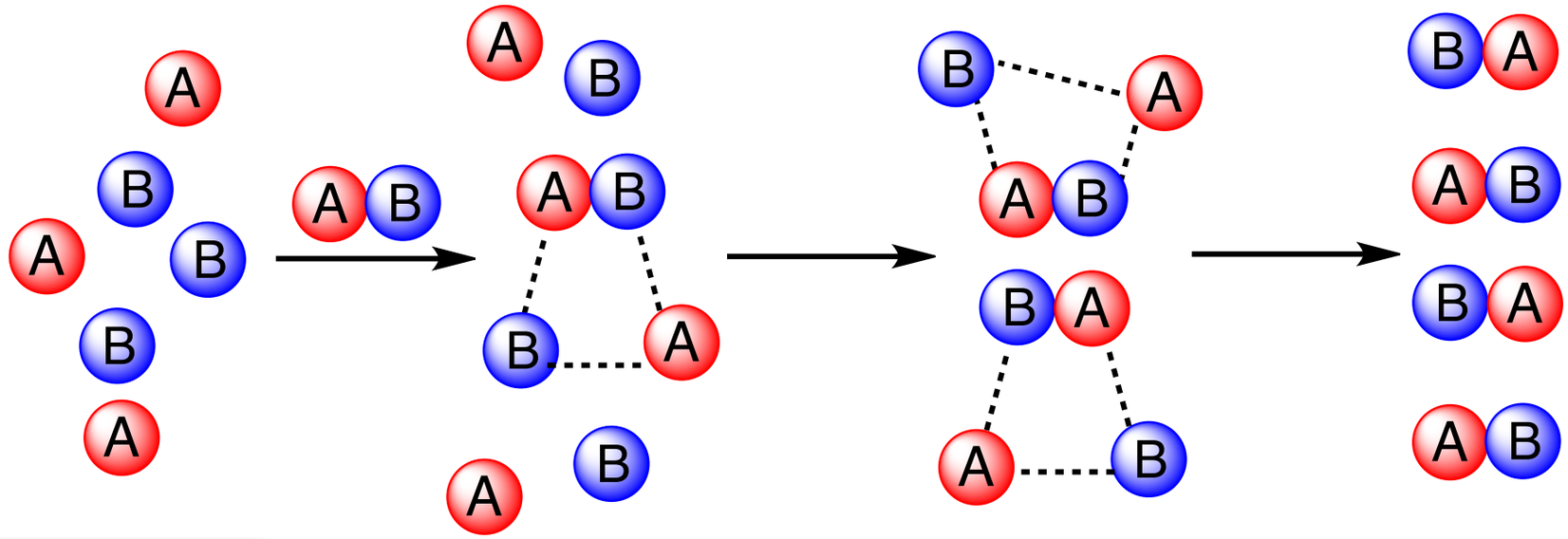


Fig.1 A simple image of autocatalysis

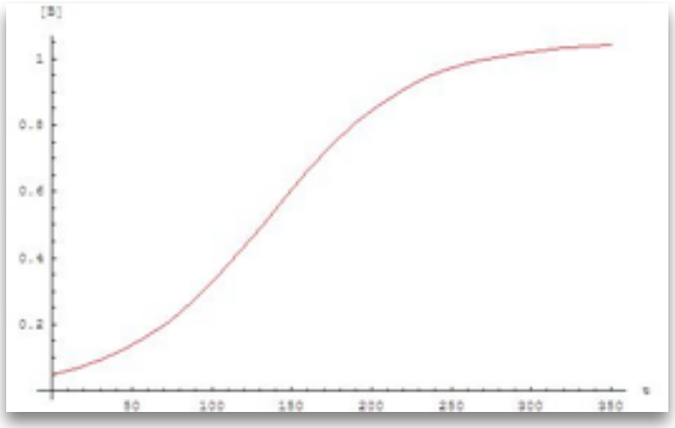


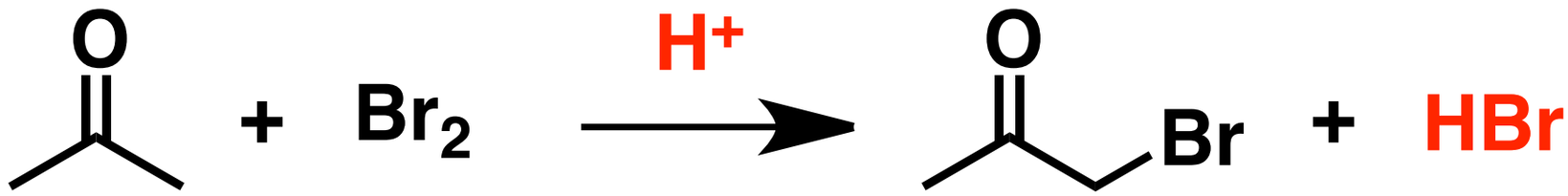
Fig.2 Sigmoid variation of product concentration in autocatalytic reactions

exponential increase of catalyst(=product)!!

Examples of Autocatalysis

- **Bromination of ketone**

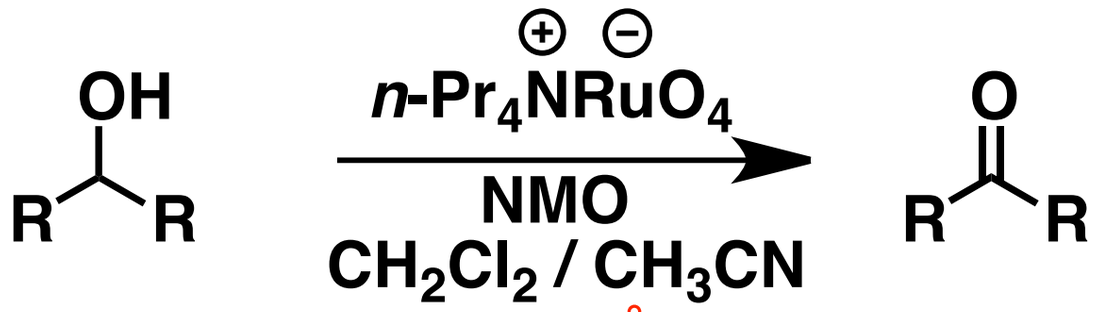
H^+ catalyzes formation of enol from ketone



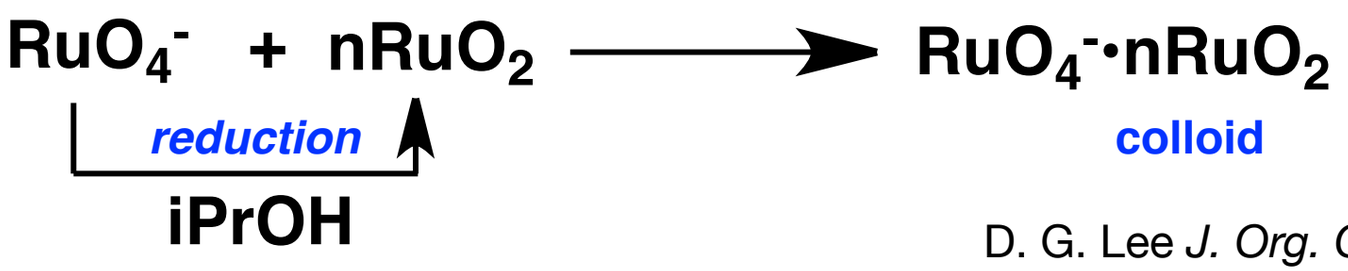
HBr regenerates catalytic H^+

- **Ley Oxidation**

water reduces autocatalysis in this reaction



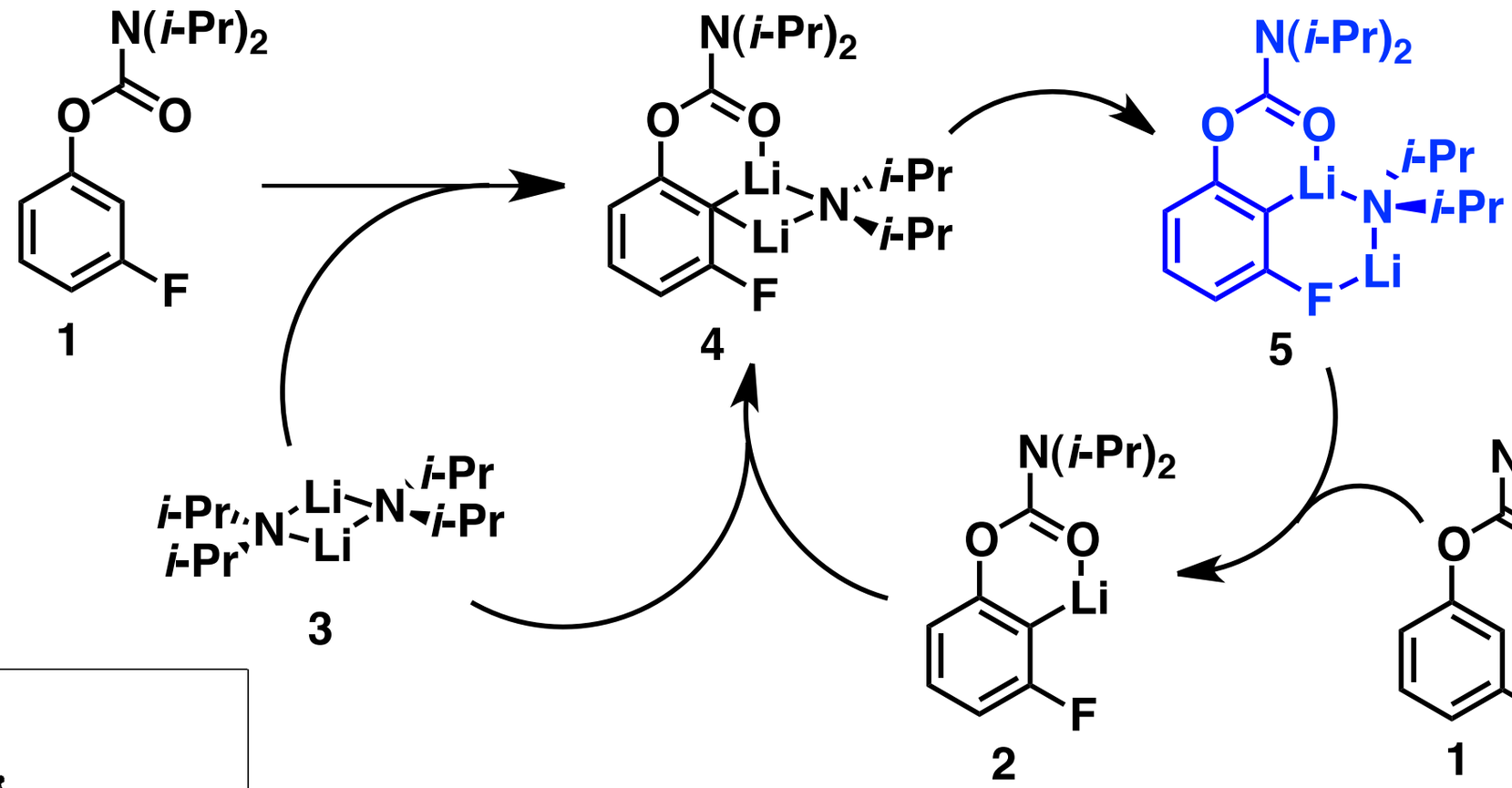
activated catalyst



D. G. Lee *J. Org. Chem.* **1992**, *57*, 3276-3277

Examples of Autocatalysis

- **LDA-Mediated Ortholithiation**



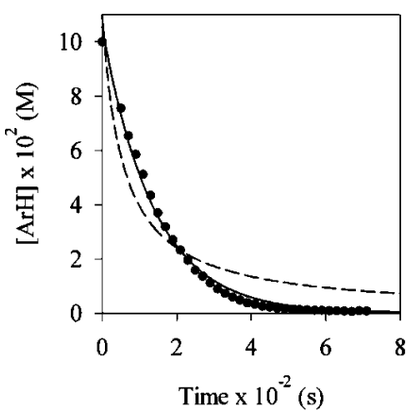


Figure 1. Reaction of 0.10 M carbamate **1** with 0.10 M LDA at −78 °C in neat THF as monitored by ^{19}F NMR spectroscopy. The solid and dashed lines represent least-squares fits to first- and second-order decays, respectively.

D. B. Collum *J. Am. Chem. Soc.* **2008**, *130*, 18008-18017

see also : D. B. Collum *J. Am. Chem. Soc.* **2010**, *132*, 15610-15623

Examples of Autocatalysis

- **Autocatalysis in Biological Systems**

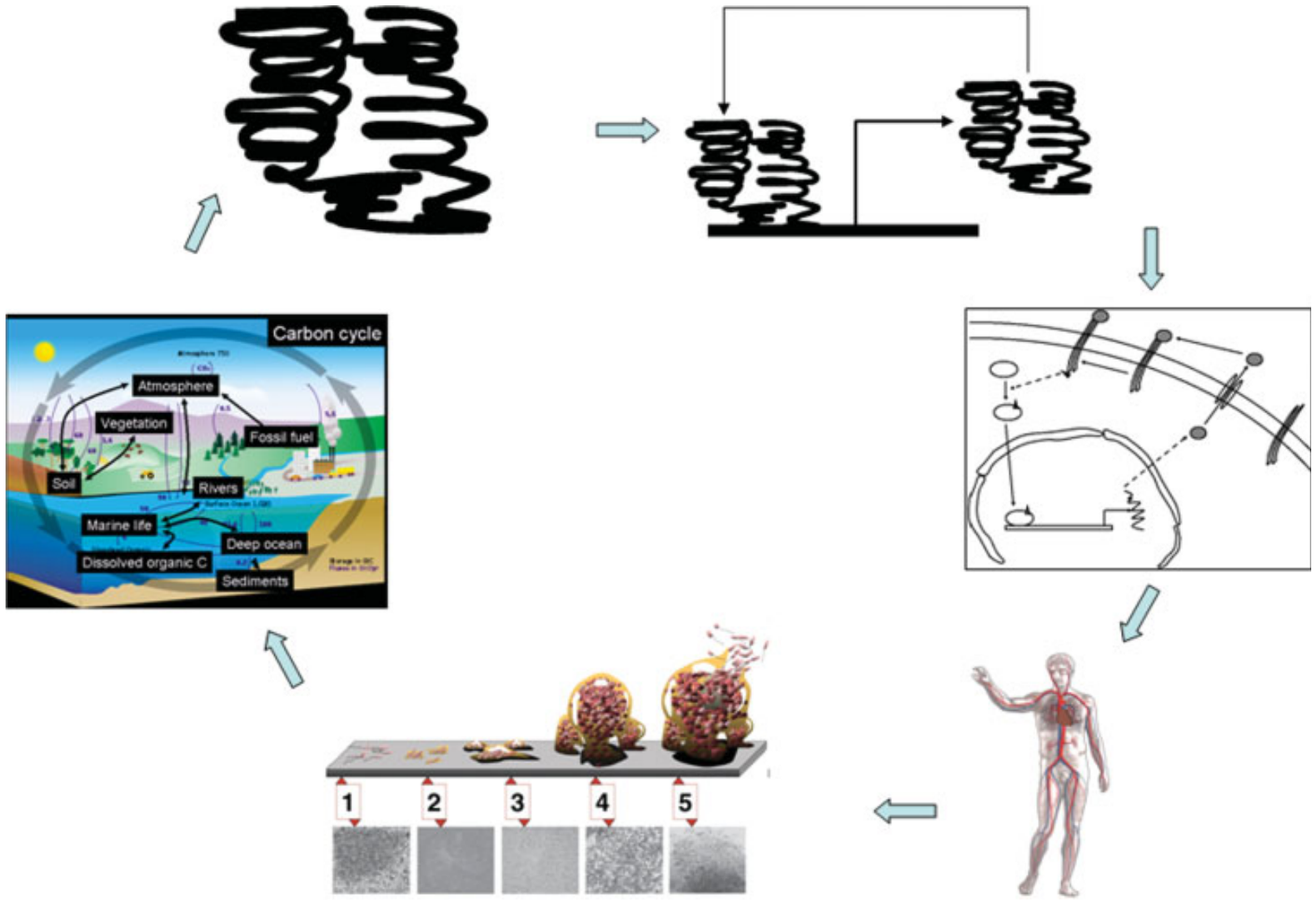


Figure 1. Autocatalysis at various scales: single molecule folding, autogeneous regulation, intracellular signaling pathways, organ systems, collective motion and ecological scales.

Evolution as a response to the environment results in changes in the structure and function of single molecules. Not shown are criss-crossing links that indicate the effect of intracellular signaling to community behavior, or single molecule folding to population dynamics for instance as seen in the effect of unfolded proteins in prion disease epidemiology. Figures except single molecule and autogeneous regulation are from wikipedia.com.

AIChE J. **2009**, *55*, 556-562

Scientific Importance

- **Chemical Oscillation**

  Belousov-Zhabotinskii(BZ) Reaction

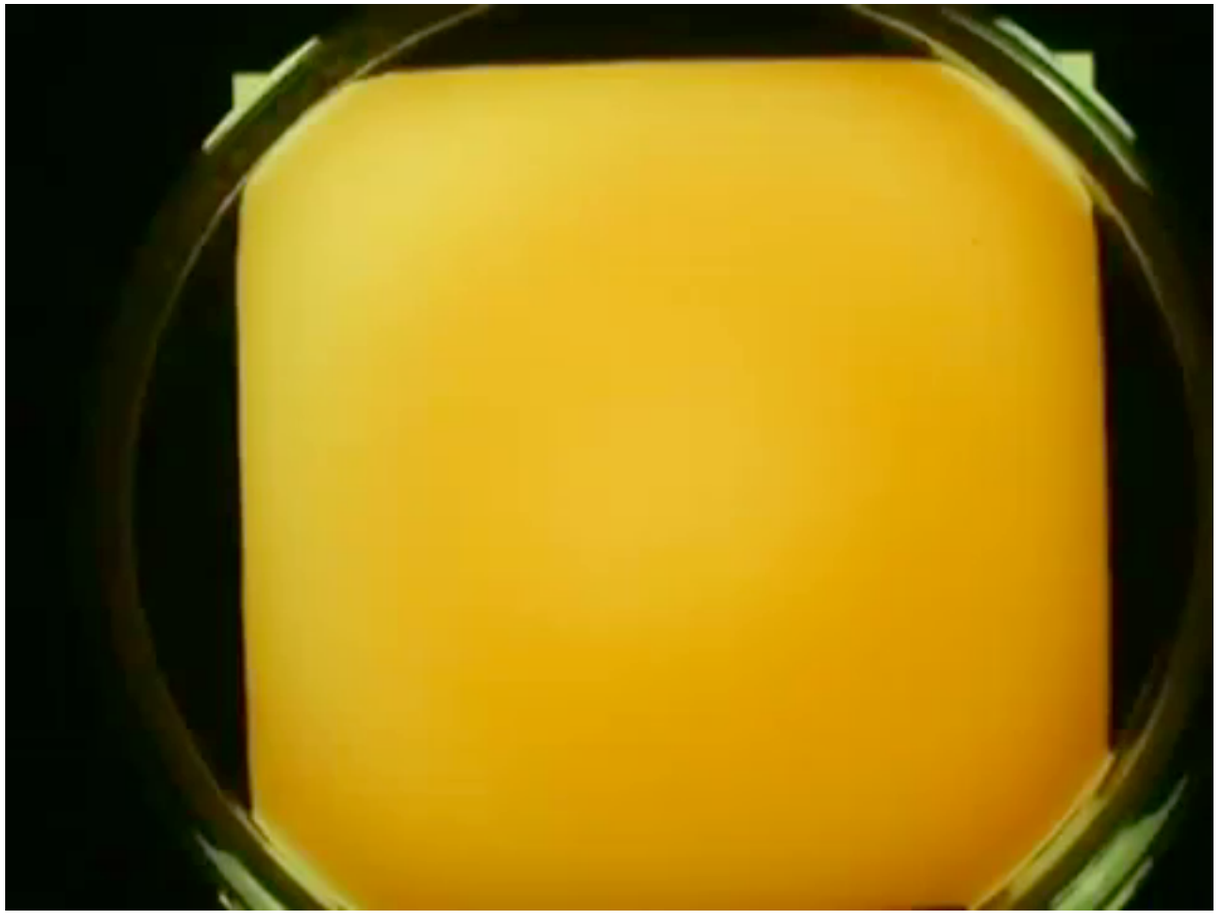


Fig.1 Change of color in BZ reaction with Ce^{3+}

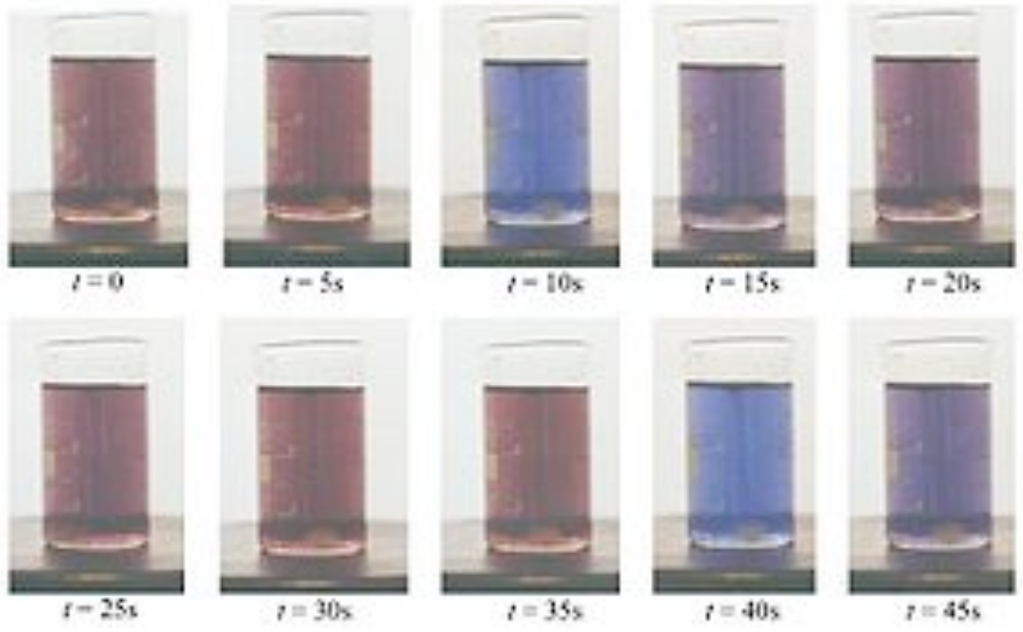


Fig.2 Change of color in BZ reaction with $Fe(phen)_3^{2+}$

Scientific Importance

- **Chemical Oscillation - BZ reaction -**

Initial step

$$Br^- + BrO_3^- + 2H^+ \longrightarrow HBrO_2 + HOBr \quad (R1)$$

$$Br^- + HOBr + H^+ \rightleftharpoons Br_2 + H_2O \quad (R2)$$

$$Br^- + HBrO_2 + H^+ \longrightarrow 2HOBr \quad (R5)$$

} ***Process A***

Autocatalytic step

$$BrO_3^- + HBrO_2 + H^+ \rightleftharpoons 2BrO_2\cdot + H_2O \quad (R3)$$

$$BrO_2\cdot + Ce^{3+} + H^+ \longrightarrow HBrO_2 + Ce^{4+} \quad (R4)$$

$$BrO_3^- + HBrO_2 + 2Ce^{3+} + 3H^+ \longrightarrow 2HBrO_2 + 2Ce^{4+} + H_2O \quad (*)$$

$$2HBrO_2 \longrightarrow HOBr + BrO_3^- + H^+ \quad (R6)$$

} ***Process B***

Oxidation of malonic acid

$$Br_2 + CH_2(CO_2H)_2 \longrightarrow BrCH(CO_2H)_2 + H^+ + Br^- \quad (R7)$$

$$6Ce^{4+} + CH_2(CO_2H)_2 + 2H_2O \longrightarrow 6Ce^{3+} + HCO_2H + CO_2 + 6H^+ \quad (R8)$$

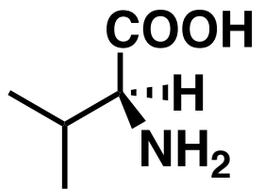
$$4Ce^{4+} + BrCH(CO_2H)_2 + 2H_2O \longrightarrow Br^- + 4Ce^{3+} + HCO_2H + CO_2 + 5H^+ \quad (R9)$$

R. J. Field, E. Körös, R. M. Noyes *J. Am. Chem. Soc.* **1972**, *94*, 8649-8664

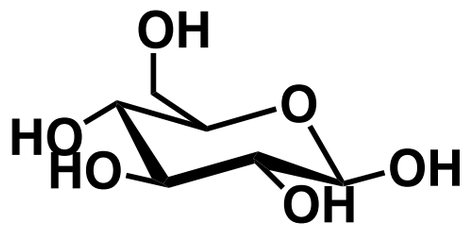
Scientific Importance

- **Origin of Life**

Homochirality

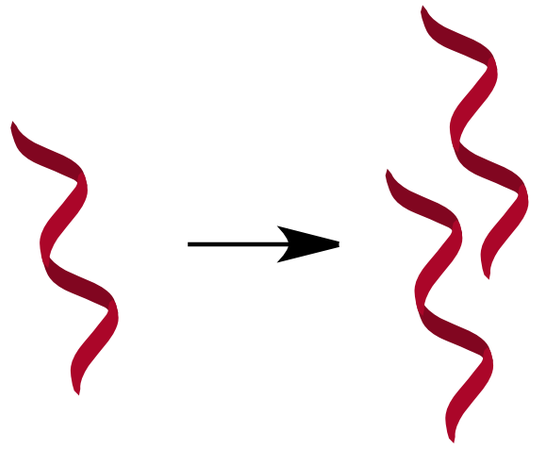


L-Valine



D-Glucose

RNA World



"Autocatalysis"

Create a New Order ?

II. Asymmetric Autocatalysis

~ Soai Reaction ~

- ✤ Asymmetric Amplification
- ✤ Discovery of Soai Reaction
- ✤ Mechanistic Study

Asymmetric Amplification

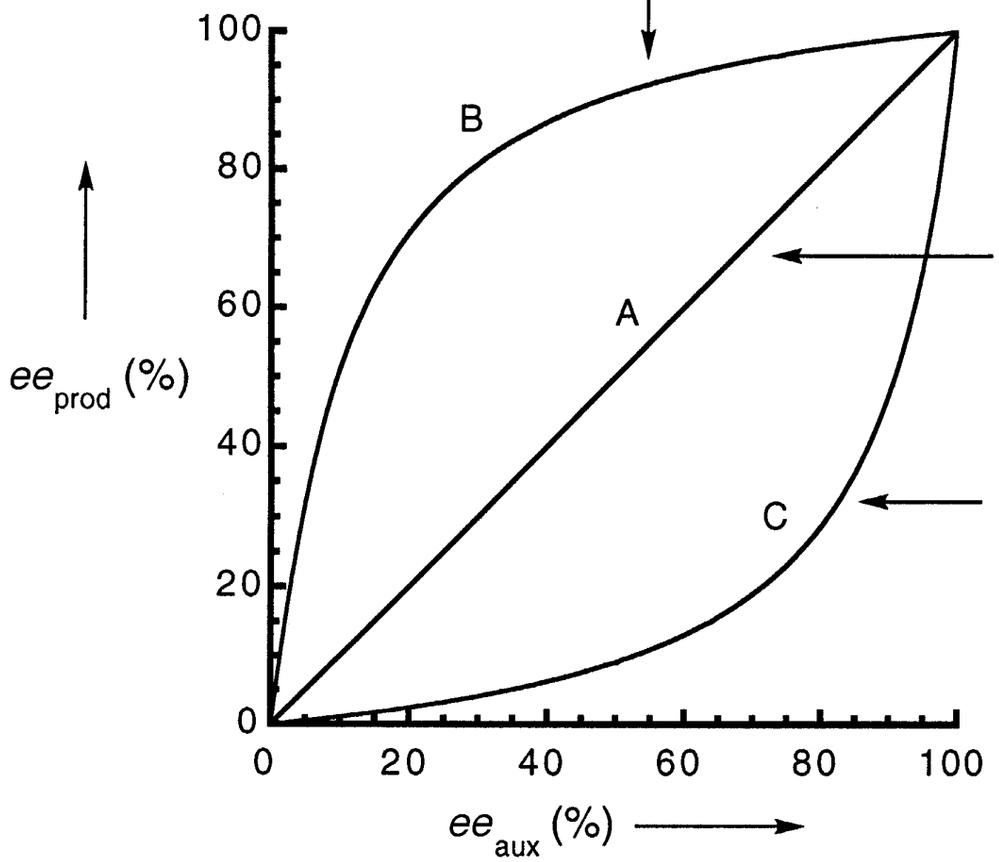
$$ee_{\mathrm{prod}} = ee_0 \cdot ee_{\mathrm{aux}}$$

ee_{prod} | *ee* value of the product

ee_0 | the maximum *ee* value of the product

ee_{aux} | *ee* value of the chiral auxiliary

(+)-nonlinear effect
(asymmetric amplification)



proportionality between
ee_{prod} and ee_{aux}

(–)-nonlinear effect
(asymmetric depletion)

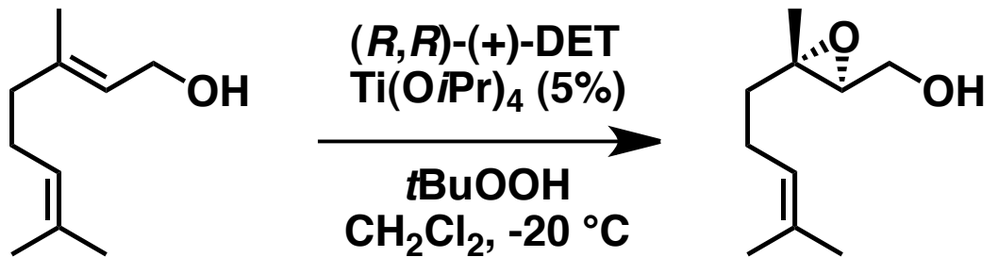
Fig.1 Non-linear effects (NLE) in asymmetric synthesis

“asymmetric amplification” means ::

$ee_{prod} > ee_0 \times ee_{aux}$

review : H. B. Kagan *Angew. Chem. Int. Ed.* **1998**, *37*, 2922-2959

Discover of (+)-/(-)-NLE



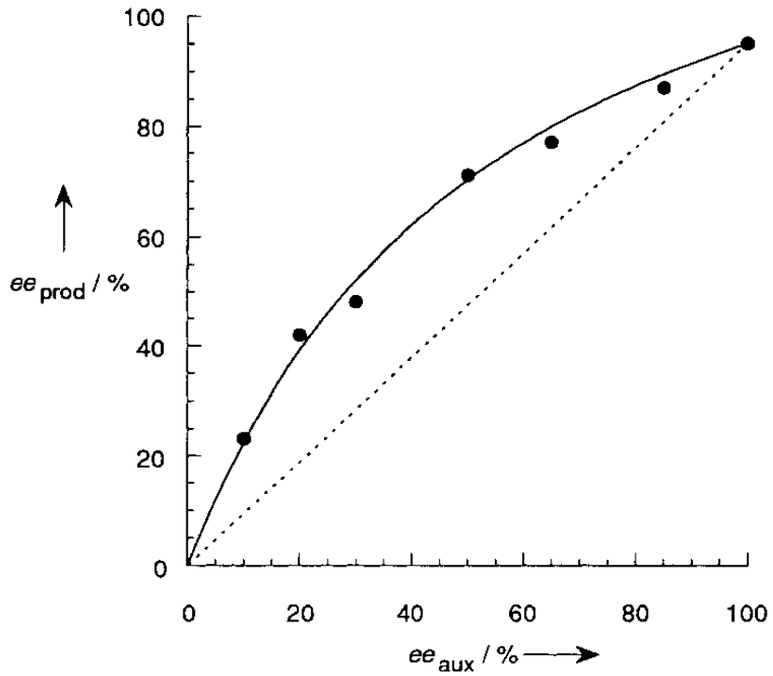
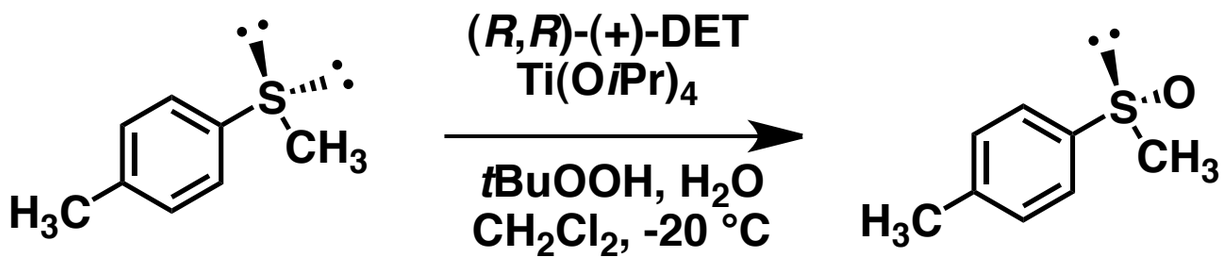


Fig.1 (+)-NLE in the Sharpless epoxidation



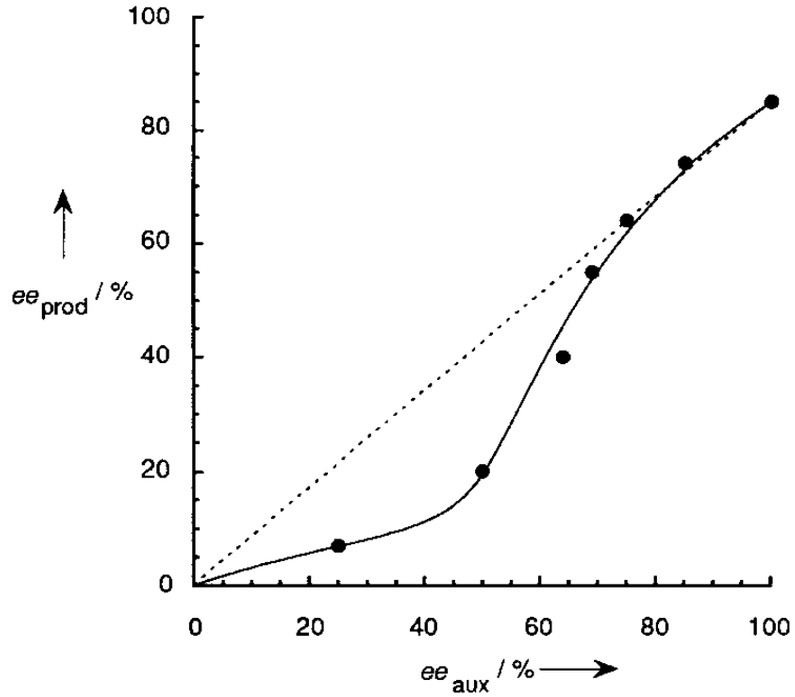


Fig.2 (-)-NLE in the asymmetric oxidation of sulfide

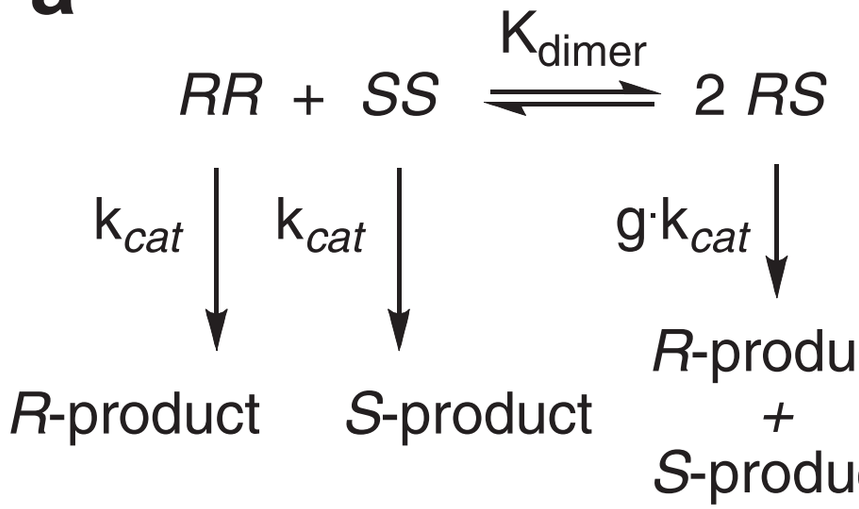
H. B. Kagan *J. Am. Chem. Soc.* **1986**, *108*, 2353-2357
H. B. Kagan *Angew. Chem. Int. Ed.* **1998**, *37*, 2922-2959

Models for Asymmetric NLE

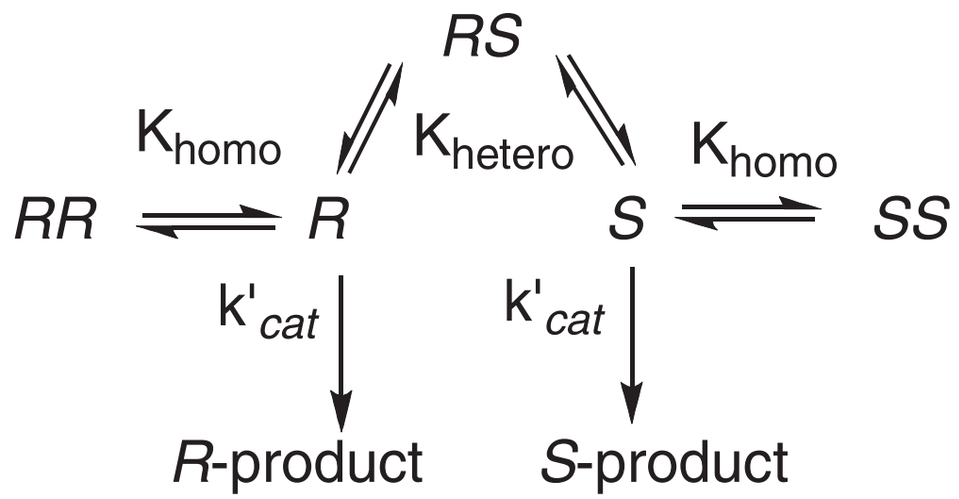

Kagan's model

Noyori's model

a



b

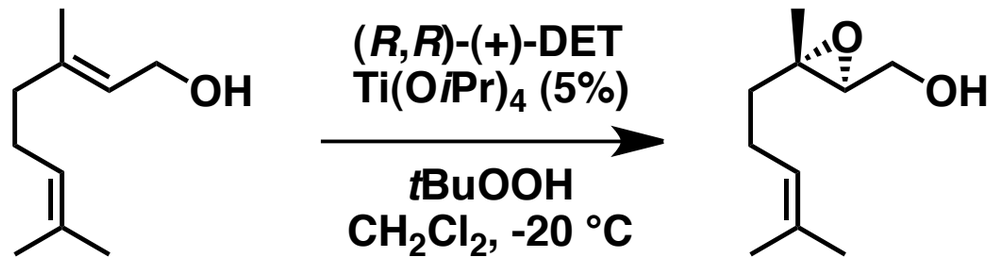


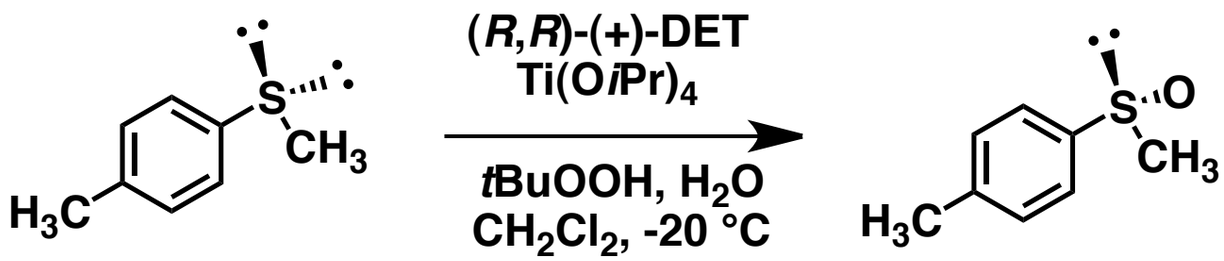
$$K_{dimer} = \left(\frac{K_{hetero}}{K_{homo}} \right)^2$$

Scheme 1. Models for non-linear effects.

D. G. Blackmond *Tetrahedron: Asymmetry* **2010**, *21*, 1630-1634

Example of (+)-/(-)-NLE





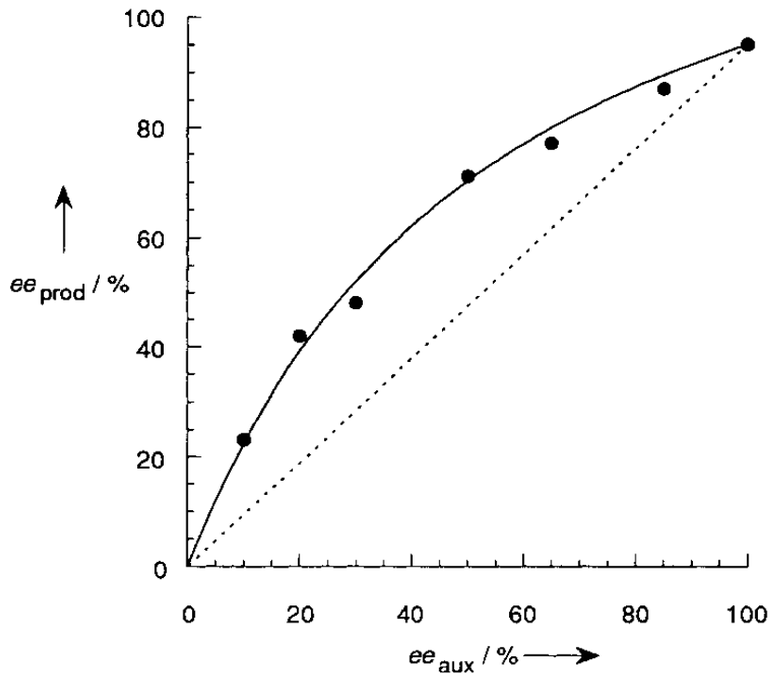


Fig.1 (+)-NLE in the Sharpless epoxidation

***EE₀* = 95%, *K* = 1000, *g* = 0.35**

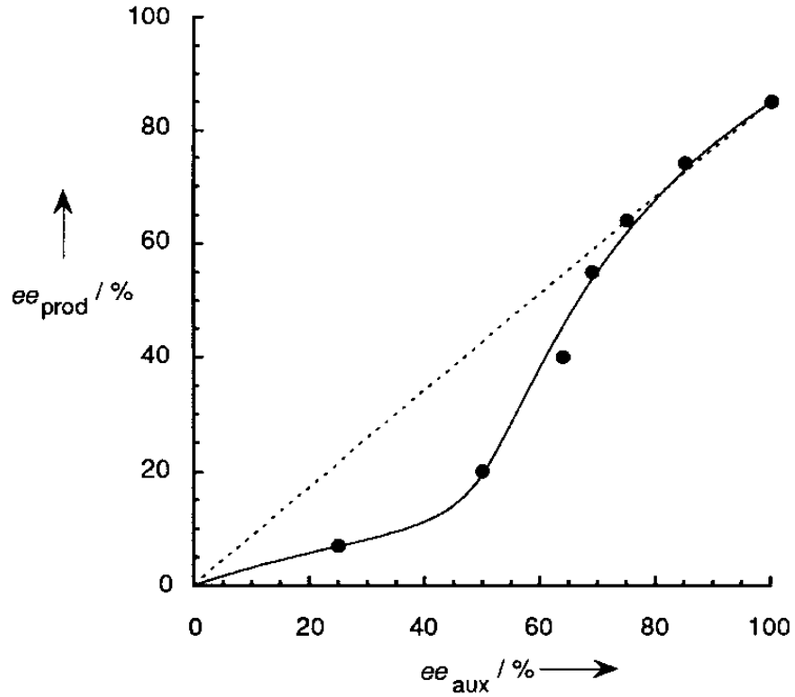


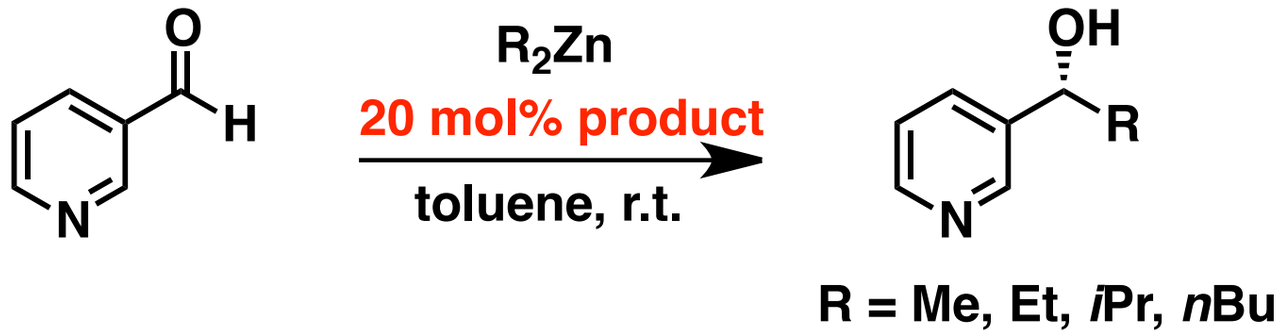
Fig.2 (-)-NLE in the asymmetric oxidation of sulfide

more complicated model is required...

H. B. Kagan *J. Am. Chem. Soc.* **1986**, *108*, 2353-2357
H. B. Kagan *Angew. Chem. Int. Ed.* **1998**, *37*, 2922-2959

Soai Reaction

- **First Asymmetric Autocatalysis**



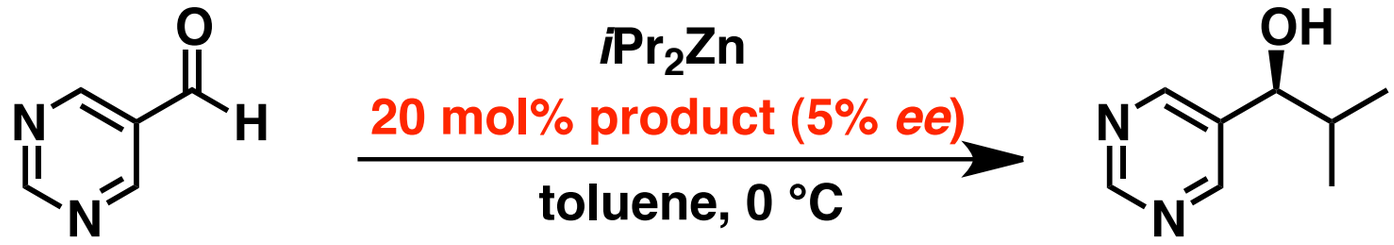
R = Me, Et, *i*Pr, *n*Bu

R	catalyst *ee* (%)	product *ee* (%)
Me	42	7
Et	56	14
*i*Pr	86	35
*n*Bu	47	6

K. Soai *J. Chem. Soc. Chem. Comm.* **1990**, 982-983

Soai Reaction

- **Asymmetric Autocatalysis *with* Amplification**



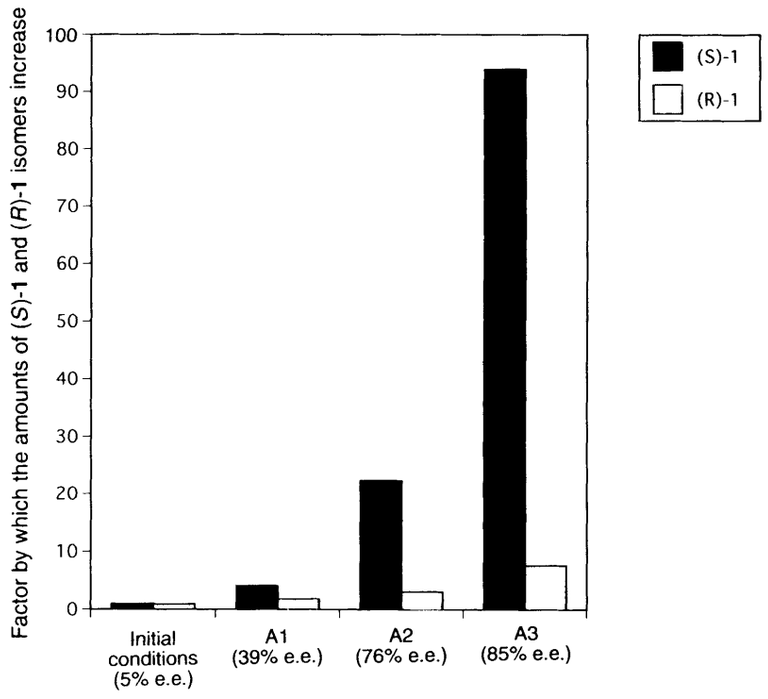


Fig.1 Asymmetric autocatalysis of chiral pyrimidyl alkanol.

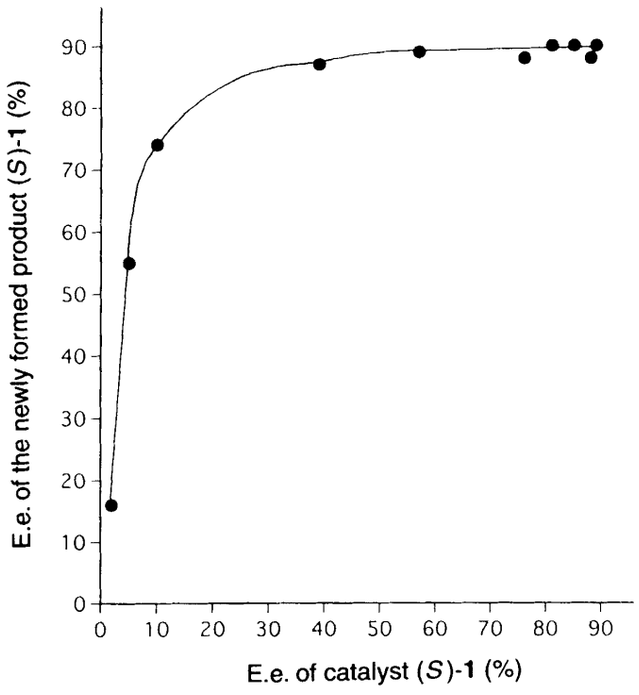
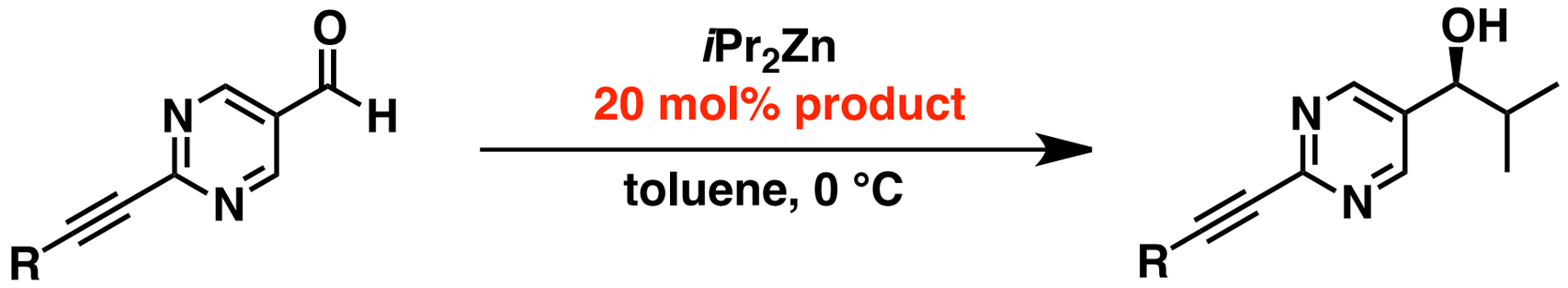


Fig.2 Relation between *ee* of catalyst and *ee* of product.

K. Soai *Nature* **1995**, *378*, 767-768

Soai Reaction

- **2-Alkynyl 5-Pyrimidyl Alkanol**

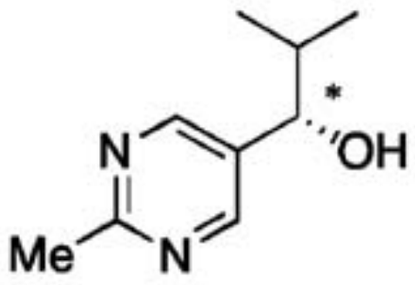


R	catalyst *ee* (%)	product *ee* (%)
*n*Bu	5.8	21.2
*t*Bu	5.5	69.6
Me_3Si	8.4	74.2
iPr_3Si	8.6	8.8
Ph	5.9	47.3

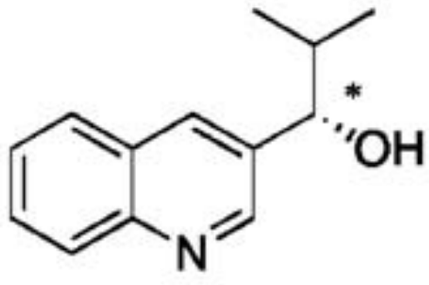
K. Soai *Angew. Chem. Int. Ed.* **1999**, *38*, 659-661

Soai Reaction

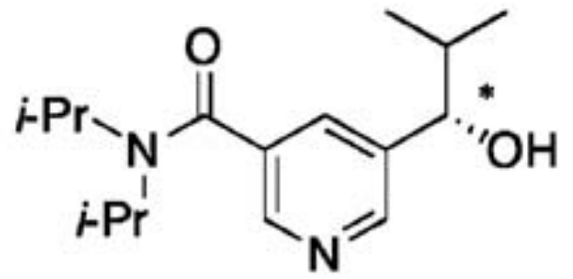
- **Other Substrates (= Catalysts !)**



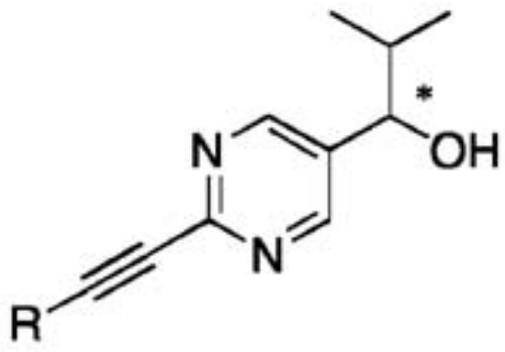
23
up to 98% ee



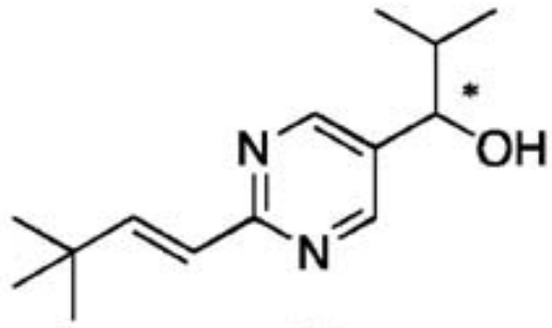
24
up to 94% ee



25
up to 86% ee



26 : R= *n*-Bu
27 : R= TMS
28 : R= Ph
29 : R= ferrocenyl

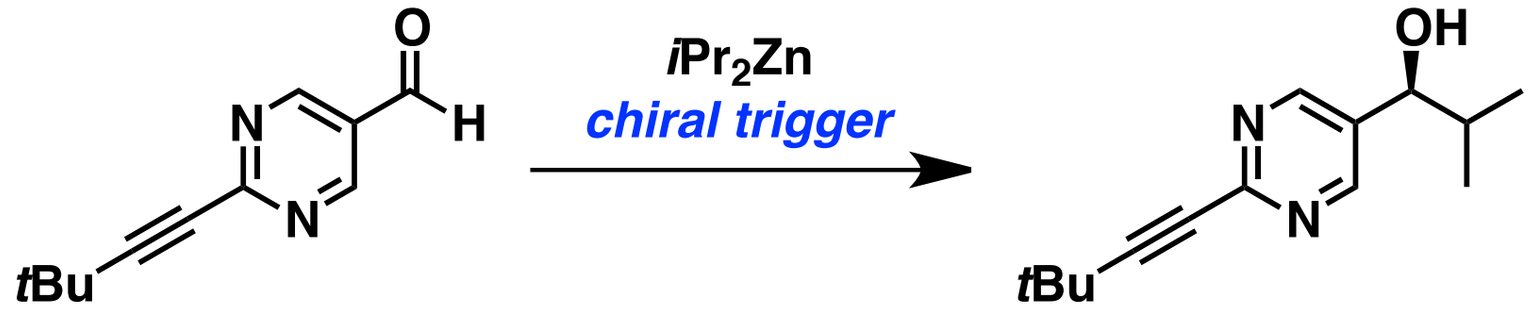


30

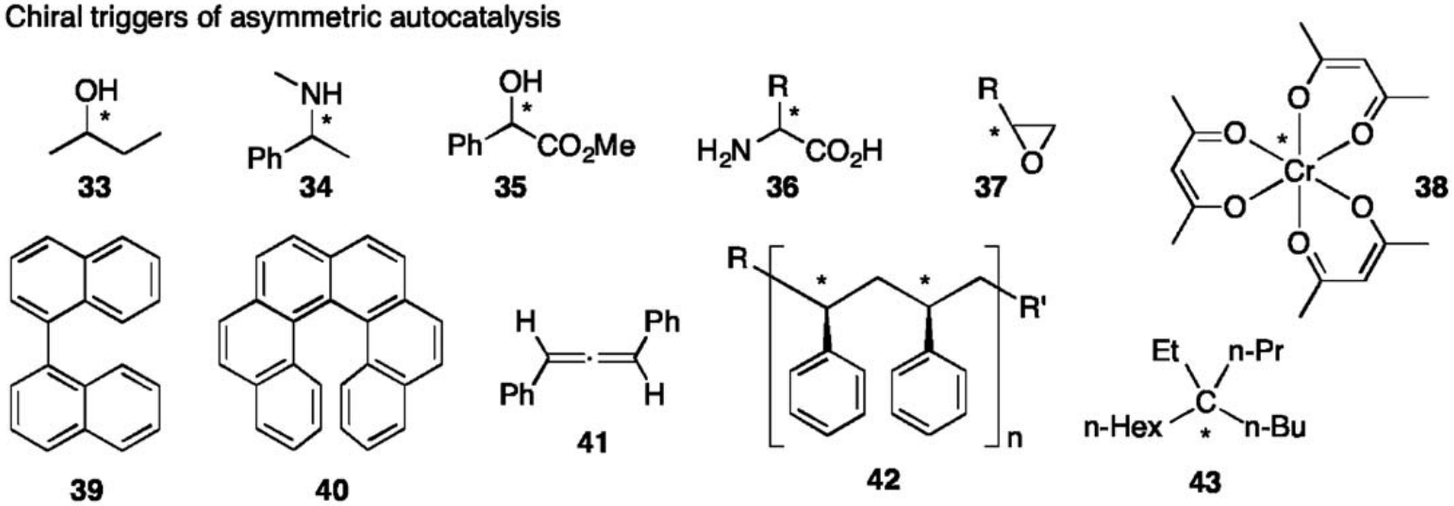
K. Soai *J. Fluorine Chem.* **2010**, *131*, 525-534

Soai Reaction

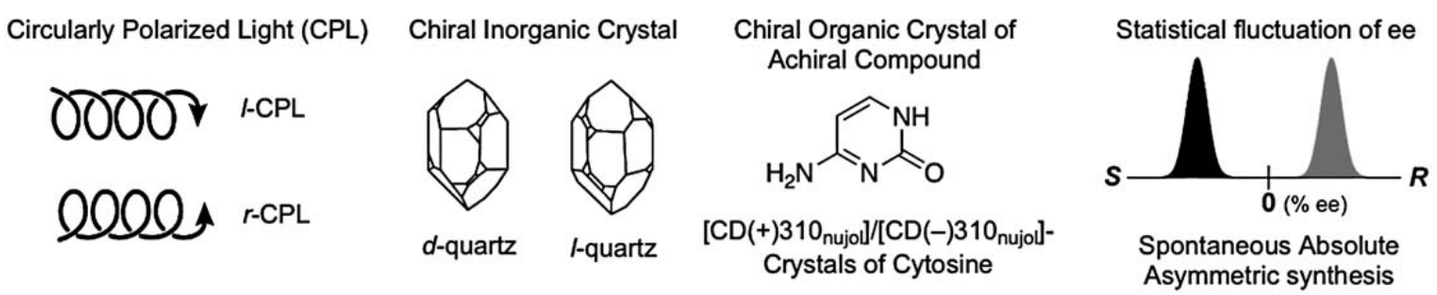
- **Various Chiral Initiators**



Chiral triggers of asymmetric autocatalysis



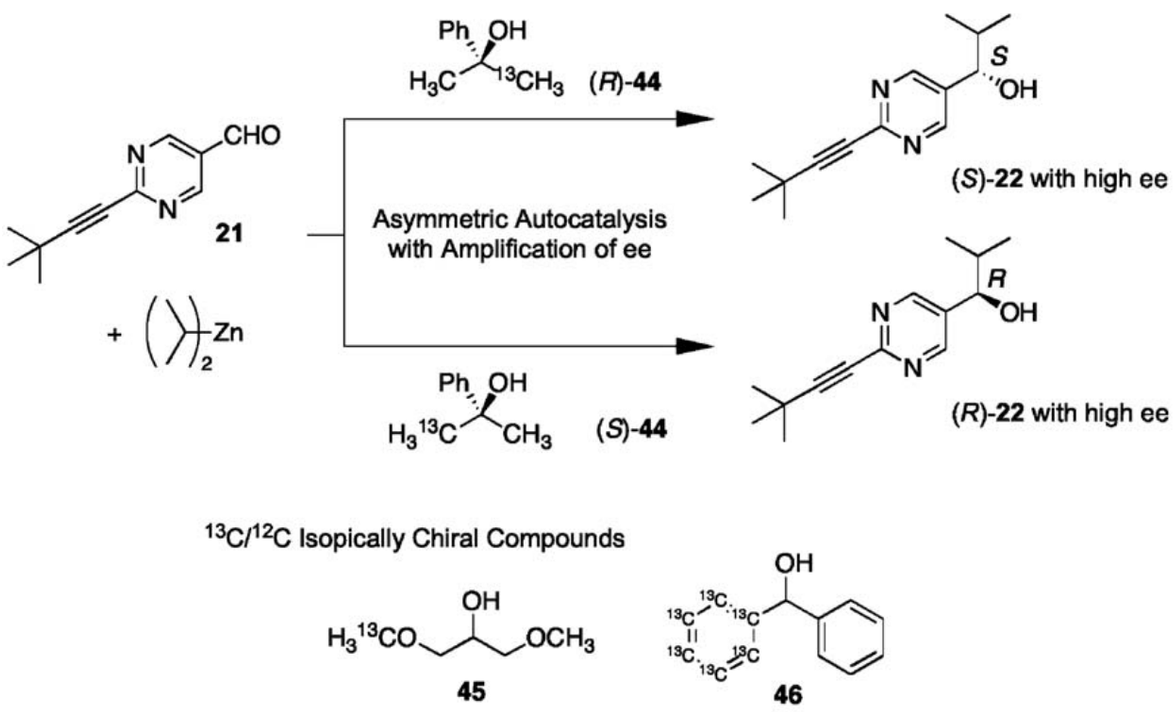
*** Proposed Origins of Chirality**

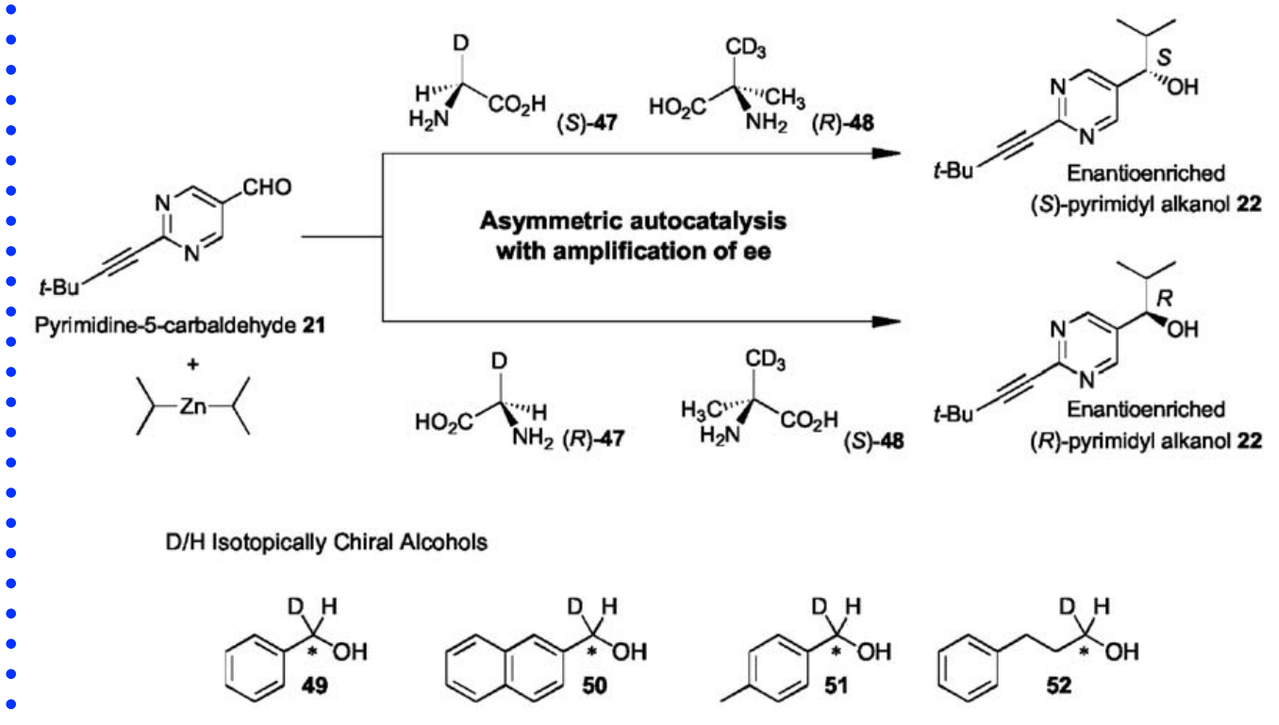


K. Soai *J. Fluorine Chem.* **2010**, *131*, 525-534

Soai Reaction

- **Isotope Chirality**





carbon isotopic effect ($^{13}C/^{12}C$)

hydrogen isotopic effect (D/H)

even isotope chirality has ability to act as a chiral trigger !

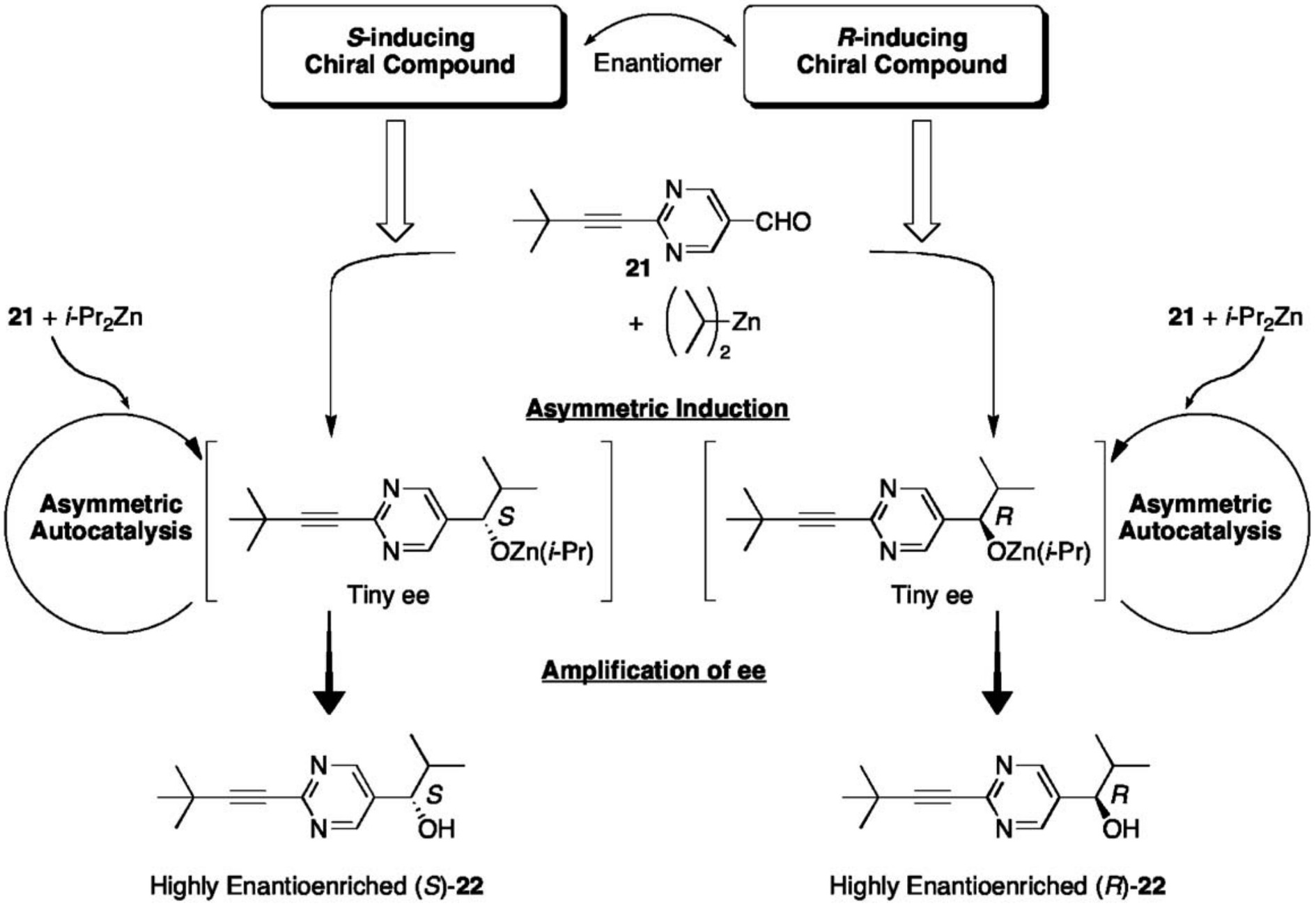
K. Soai *J. Am. Chem. Soc.* **2000**, *122*, 11739-11740

K. Soai *Chem. Comm.* **2009**, 4396-4398

K. Soai *Science* **2009**, *324*, 492-495

K. Soai *J. Fluorine Chem.* **2010**, *131*, 525-534

Summary of Soai Reaction



K. Soai *J. Fluorine Chem.* **2010**, *131*, 525-534

Mechanism of Soai Reaction

- **Autocatalysis Alone**

$$ee_{\text{prod}} = ee_0 \cdot ee_{\text{aux}}$$

ee_{prod} | *ee* value of the product

ee_0 | the maximum *ee* value of the product

ee_{aux} | *ee* value of the chiral auxiliary

If the catalyst is NOT perfect ($ee_0 < 1$) , the product ee will be less than catalyst ee and the lower ee products will be serving as catalysts in future reactions!

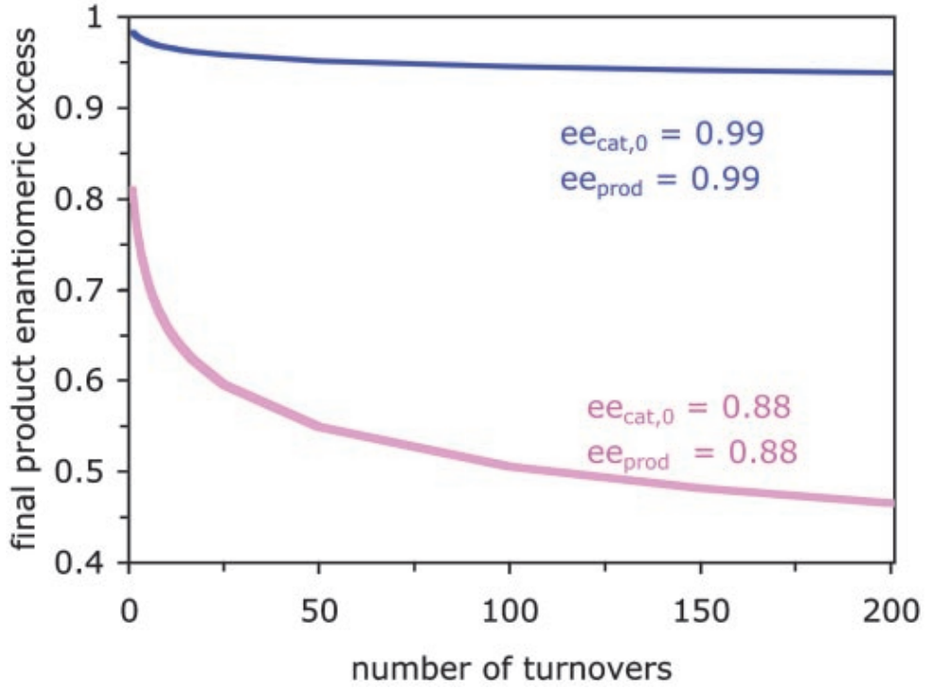


Fig. 1. Simple asymmetric autocatalytic reactions (unlike the Soai reaction) necessarily show an erosion of ee over time. Plotted is the final product ee as a function of turnover number in asymmetric autocatalytic reactions for two hypothetical of autocatalysts at different ee and different product enantioselectivity: a catalyst with an initial $ee_{cat,0} = 0.99$ exhibiting an enantioselectivity of 0.99 (solid blue line), and a catalyst with an initial $ee_{cat,0} = 0.88$ exhibiting an enantioselectivity of 0.88 (shaded magenta line).

$$ee_{\text{prod,f}} = ee_{\text{cat,0}} \cdot (\text{TON} + 1)^{(ee_0 - 1)}.$$

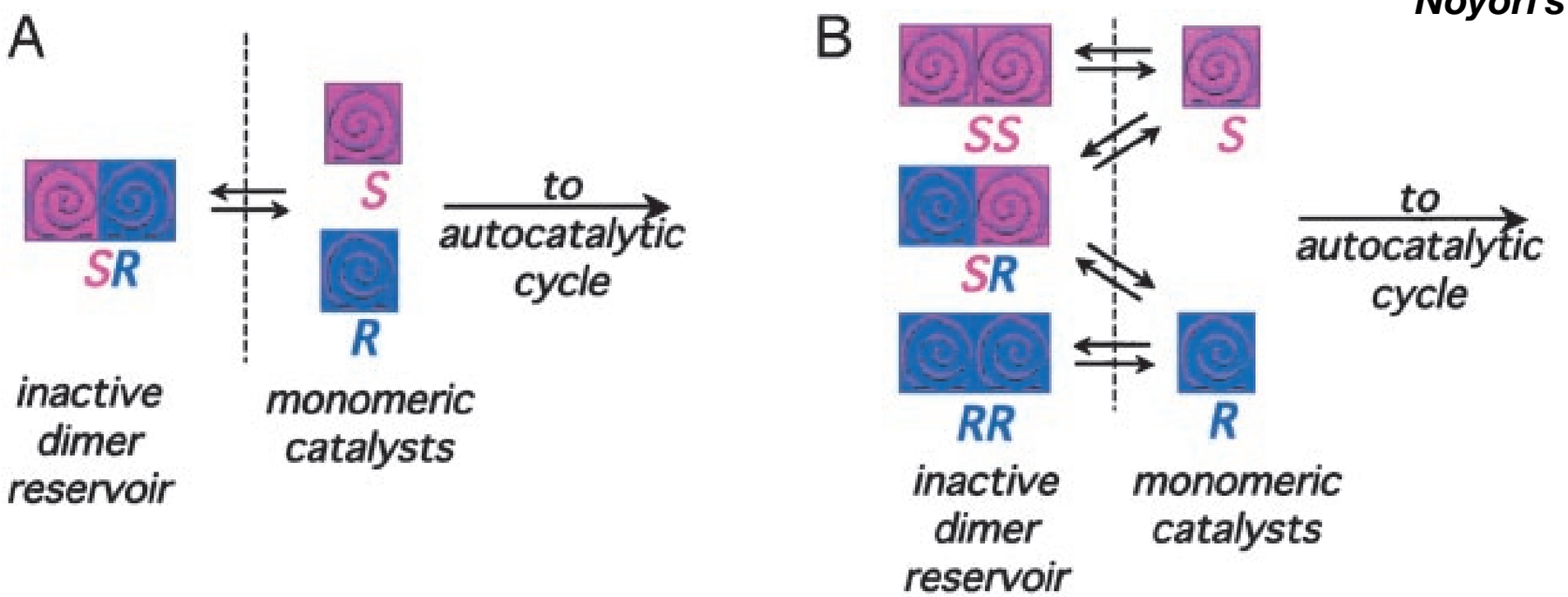
D. G. Blackmond *Proc. Nat. Acad. Sci. USA* **2004**, *101*, 5732-5736

Mechanism of Soai Reaction

- **Mutual Antagonism**

"anticatalyst" : autocatalyst must be capable not only of producing itself but also of suppressing

Noyori's model



Scheme 2. Models for including mutual antagonism in autocatalytic systems. (*A*) Specific mutual antagonism: enantiomeric *R* and *S* catalysts form a reservoir of inactive heterochiral dimers. If the initial ratio of *S*:*R* enantiomers is not 1:1, a greater fraction of the minor enantiomer is extracted into the dimer reservoir, which has total *S*:total *R* ratio equal to 1:1. (*B*) Unspecific mutual antagonism: enantiomeric *R* and *S* catalysts form a reservoir of inactive homochiral and heterochiral dimers in statistical proportions.

D. G. Blackmond *Proc. Nat. Acad. Sci. USA* **2004**, *101*, 5732-5736

Mechanism of Soai Reaction

- **A Paradox Emerges**

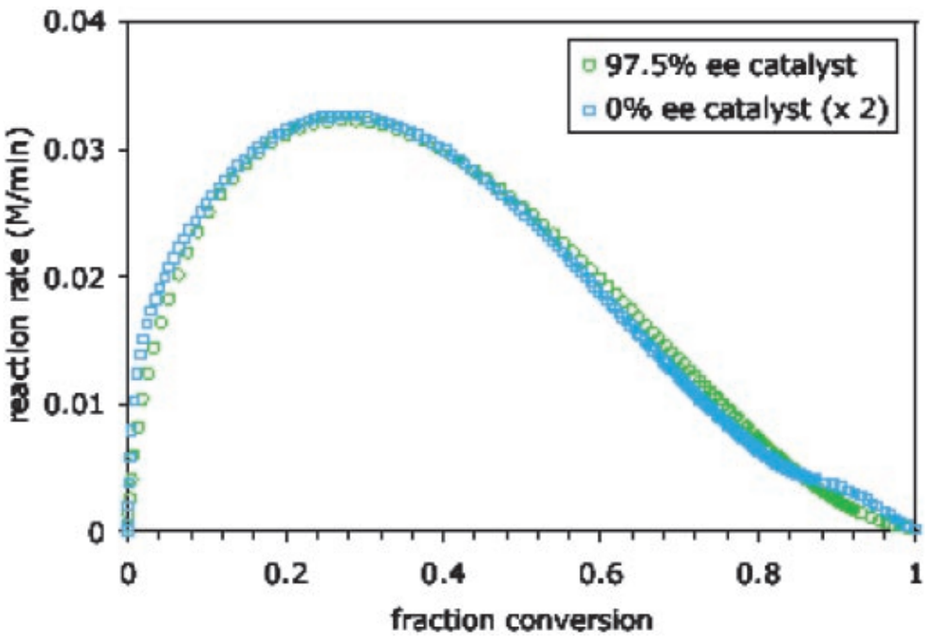


Fig. 2. Experimental reaction rate as a function of fraction conversion of the aldehyde 1b in the Soai autocatalytic reaction shown in Scheme 1 employing enantiopure and racemic catalyst. The experimental rate for the racemic catalyst has been multiplied by a factor of ≈2 (1.93).

Racemic rate should start to lag behind the enantiopure (due to heterodimer) to cause an amplification in *ee*.

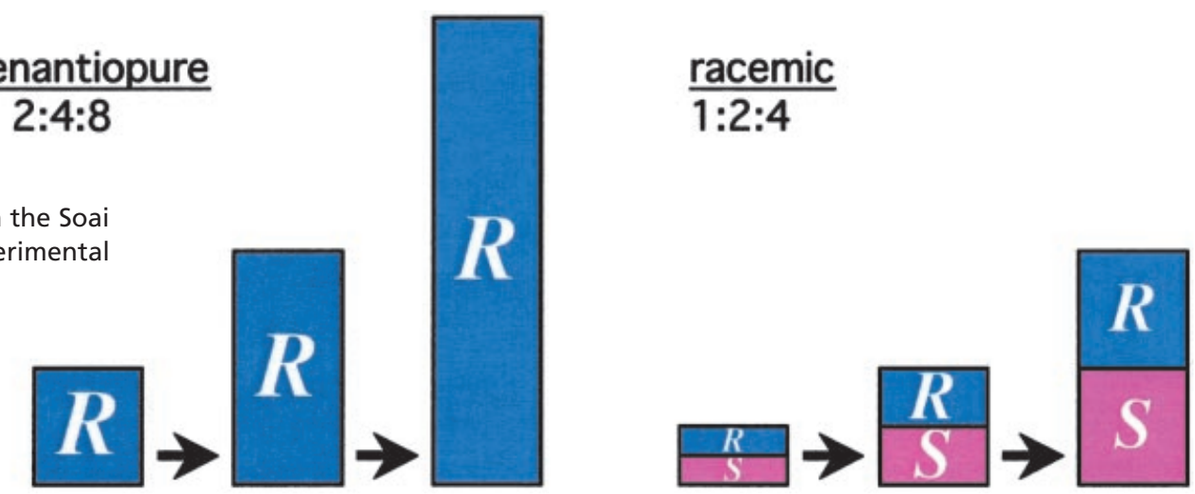


Fig. 3. Schematic depicting how the catalyst concentration increases for enantiopure and racemic catalysts as the autocatalytic reaction of Scheme 1 proceeds, as predicted by the experimentally measured reaction rates shown in Fig. 2.

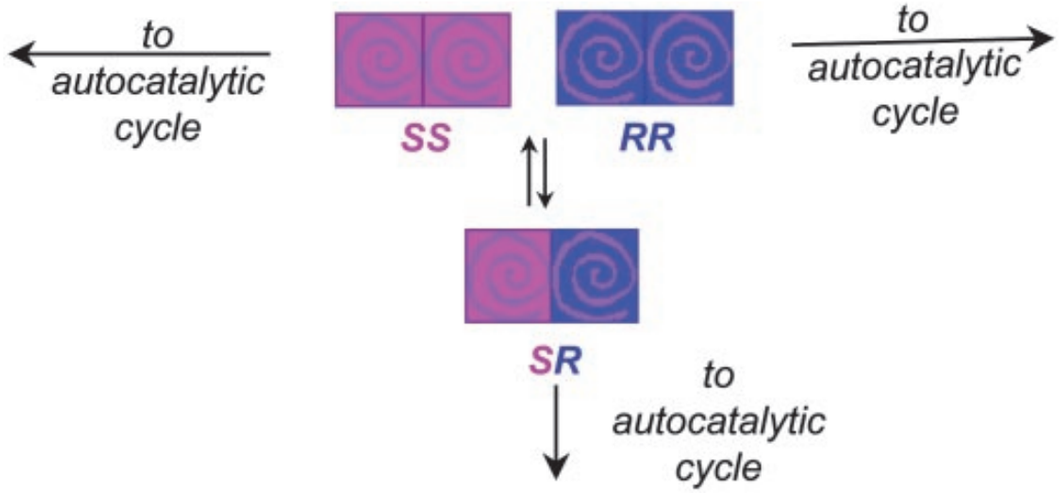
Paradox:
the rate data fit a model that says there should be no asymmetric amplification in *ee*; but amplification in *ee* is the very phenomenon that is the hallmark of the Soai reaction system !

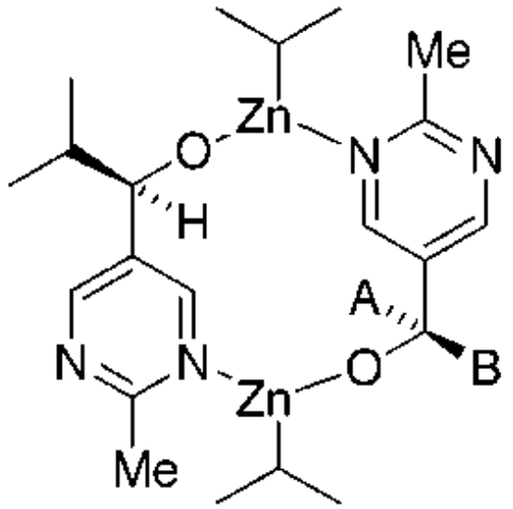
D. G. Blackmond *Proc. Nat. Acad. Sci. USA* **2004**, *101*, 5732-5736

Mechanism of Soai Reaction

- **Solution: Dimeric Catalyst**

Kagan's ML_2 model





***(S,S)*-8** A = H, B = Pr^i
***(R,S)*-8** A = Pr^i, B = H

Scheme 3. ML_2 model for autocatalysis. The monomeric *R* and *S* enantiomers form homochiral (*RR* and *SS*) and heterochiral (*SR*) dimers that themselves serve as the active catalysts in the autocatalytic reaction.

the hybrid dimer model explains the rate data perfectly

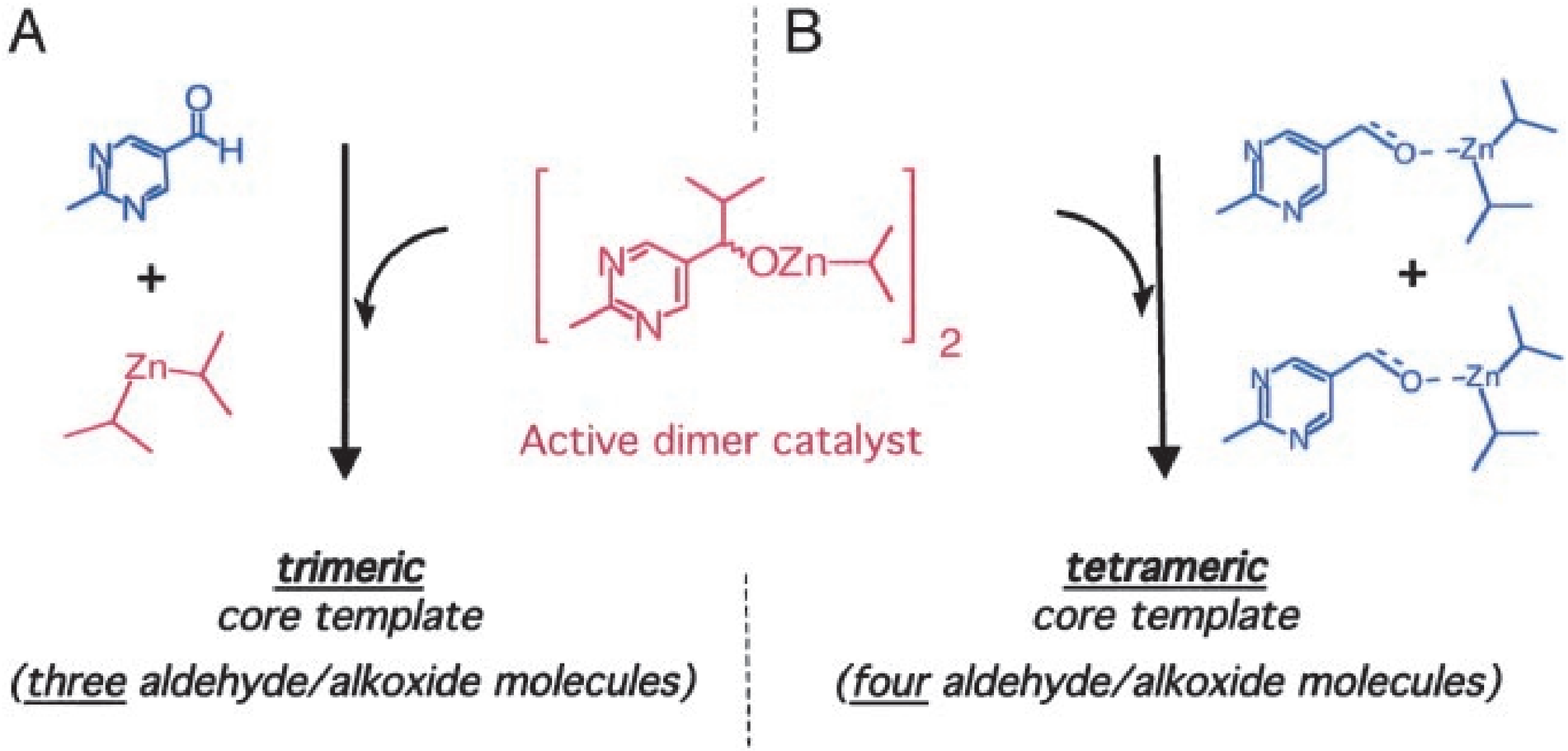
All we need to assume to explain the amplification of ee is that the homochiral species is better at catalyzing the reaction than is the heterochiral species.

D. G. Blackmond *J. Am. Chem. Soc.* **2001**, *123*, 10103-10104
D. G. Blackmond *Proc. Nat. Acad. Sci. USA* **2004**, *101*, 5732-5736

Mechanism of Soai Reaction

- **Additional Mechanistic Evidence**

rate = k[aldehyde][*i*Pr$_2$Zn][homochiraldimer] ⟶ rate = k'[aldehyde]^2[homochiraldimer]

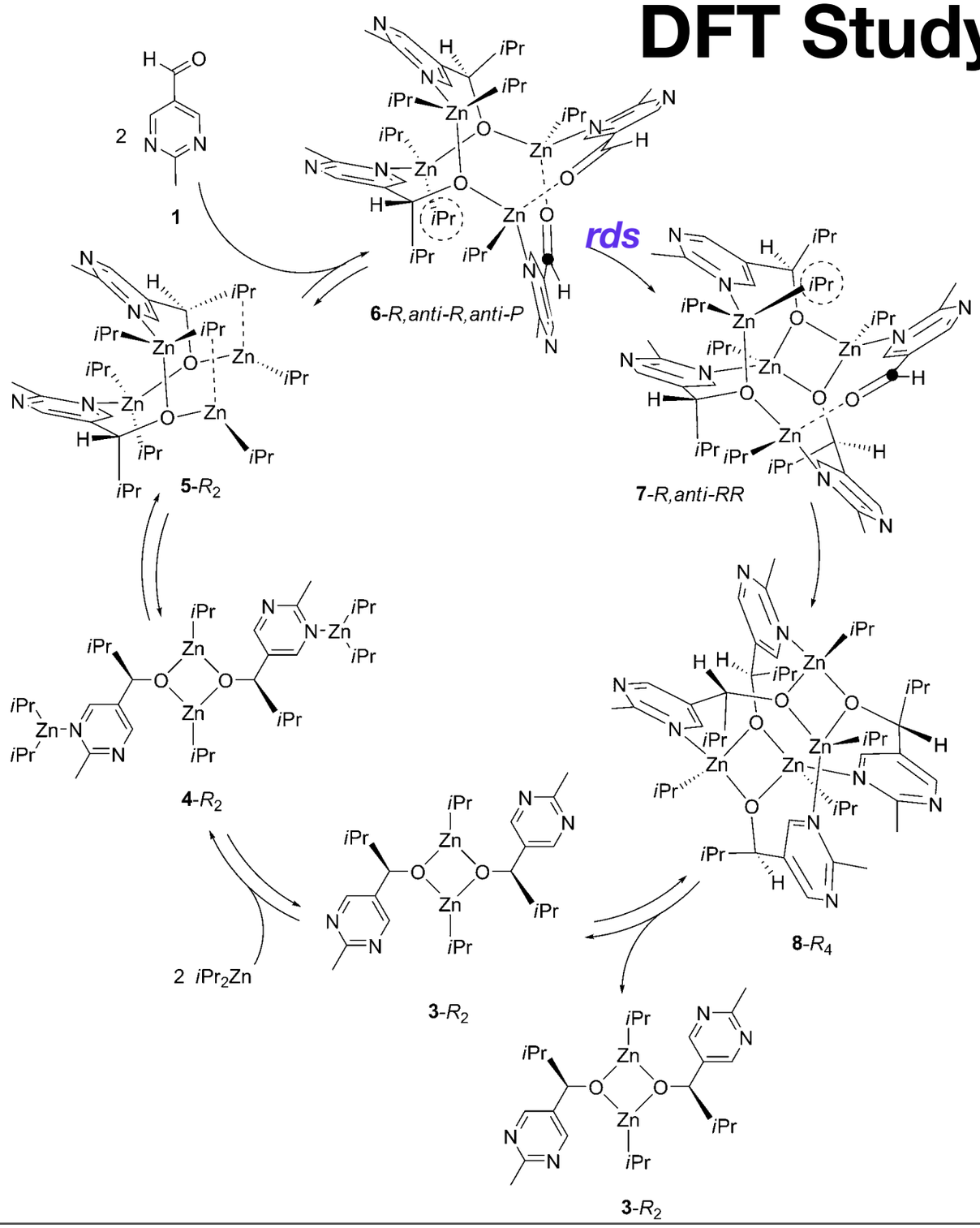


Scheme 4. Proposed models for the Soai reaction based on trimeric (*A*) and tetrameric (*B*) transition states, where the order refers to the number of prochiral aldehyde plus ex-aldehyde (alcohol/alkoxide or nascent alkoxide species) that are brought together (although not simultaneously) in the reaction event.

D. G. Blackmond *J. Am. Chem. Soc.* **2003**, *125*, 8978-8979
D. G. Blackmond *Proc. Nat. Acad. Sci. USA* **2004**, *101*, 5732-5736

Mechanism of Soai Reaction

DFT Study Suggests a Mechanism



$$R_2 + 2\,Z \rightleftharpoons (R_2Z_2)^{I} \qquad S_2 + 2\,Z \rightleftharpoons (S_2Z_2)^{I}$$

$$(R_2Z_2)^{I} \rightleftharpoons (R_2Z_2)^{II} \qquad (S_2Z_2)^{I} \rightleftharpoons (S_2Z_2)^{II}$$

$$(R_2Z_2)^{II} + 2\,A \rightleftharpoons R_2Z_2A_2 \qquad (S_2Z_2)^{II} + 2\,A \rightleftharpoons S_2Z_2A_2$$

$$R_2Z_2A_2 \xrightarrow{slow} R_3ZA \qquad S_2Z_2A_2 \xrightarrow{slow} S_3ZA$$

$$R_3ZA \rightarrow R_4 \qquad S_3ZA \rightarrow S_4$$

$$R_4 \rightleftharpoons 2\,R_2 \qquad S_4 \rightleftharpoons 2\,S_2$$

$$R_2 + S_2 \rightleftharpoons 2\,RS$$

$$(R_2Z_2)^{I} + (S_2Z_2)^{I} \rightleftharpoons 2\,(RSZ_2)^{I}$$

$$(R_2Z_2)^{II} + (S_2Z_2)^{II} \rightleftharpoons 2\,(RSZ_2)^{II}$$

Scheme 2. Proposed mechanism for the Soai autocatalytic reaction.

This mechanism is consistent with kinetic results

G. Ercolani *Chem. Eur. J.* **2010**, *16*, 3147-3156

III. Organic Autocatalysis

~ Synthetic Autocatalyst ~

- ✤ Self-Replicating System
- ✤ Ability to Catalyze Other Reaction

Replication Models

Minimal model

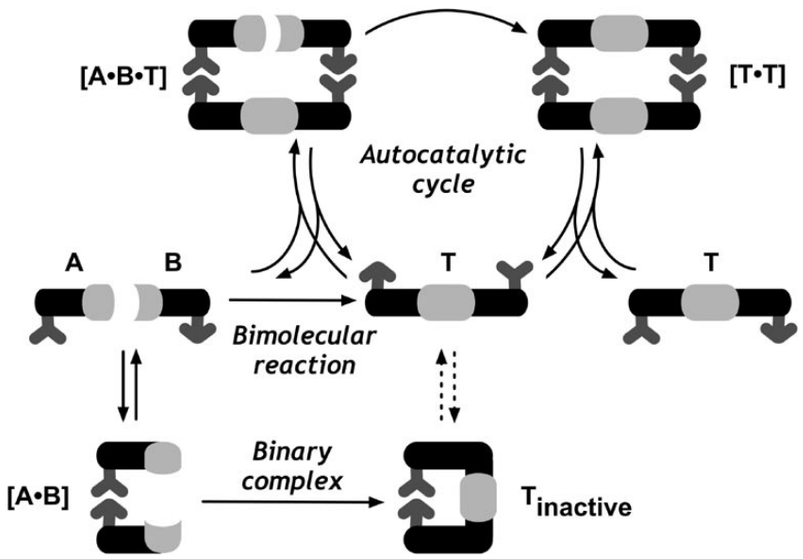


Figure 1. The minimal model of self-replication. Reagents **A** and **B** can react through three pathways – an uncatalyzed bimolecular reaction, a recognition-mediated pseudounimolecular pathway mediated by a binary complex [**A·B**] and a recognition-mediated pseudounimolecular autocatalytic cycle mediated by a ternary complex [**A·B·T**].

Reciprocal model

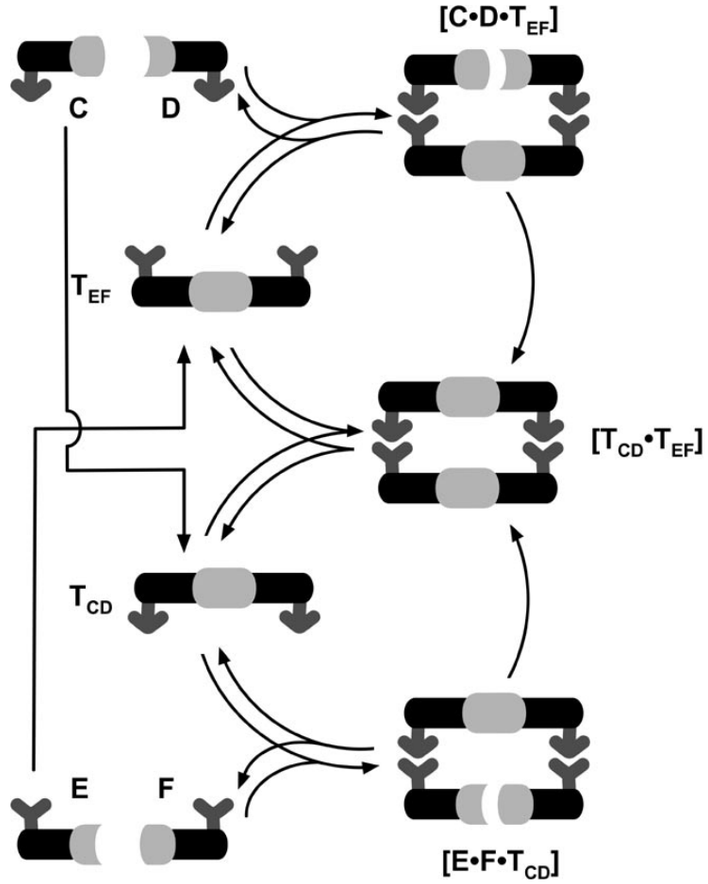
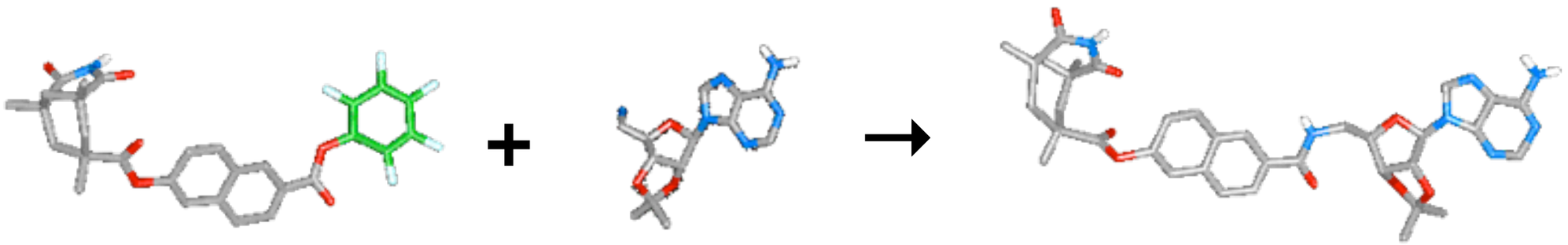


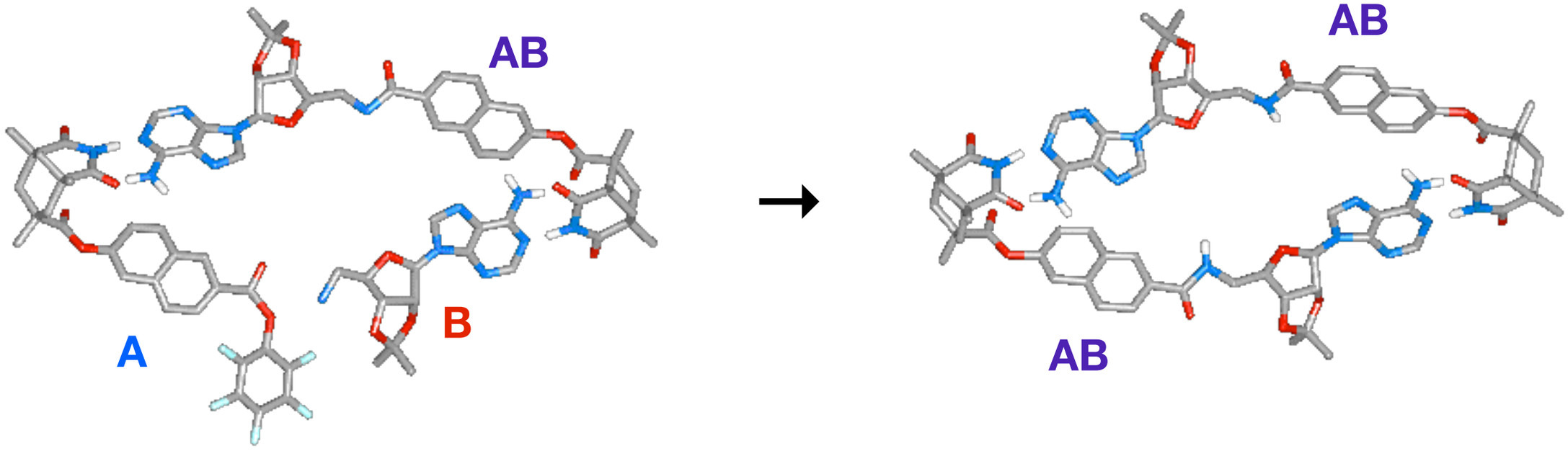
Figure 2. The reciprocal model of self-replication. Compounds **C** and **D** can react to form the template $\mathbf{T_{CD}}$, and, similarly, compounds **E** and **F** can react to form template $\mathbf{T_{EF}}$. $\mathbf{T_{CD}}$ and $\mathbf{T_{EF}}$ are mutually complementary. $\mathbf{T_{CD}}$ is capable of assembling **E** and **F** into the ternary complex [$\mathbf{E{\cdot}F{\cdot}T_{CD}}$] which catalyses the formation of $\mathbf{T_{EF}}$. Similarly, $\mathbf{T_{EF}}$ is capable of assembling **C** and **D** into the ternary complex [$\mathbf{C{\cdot}D{\cdot}T_{EF}}$] catalyzing the formation of $\mathbf{T_{CD}}$. These two interlinked cross-catalytic cycles represent a formal reciprocal replication cycle.

D. Philip *Eur. J. Org. Chem.* **2009**, 593-610

The Art of Self-Replicator

有機化学美術館
The Museum of Organic Chemistry

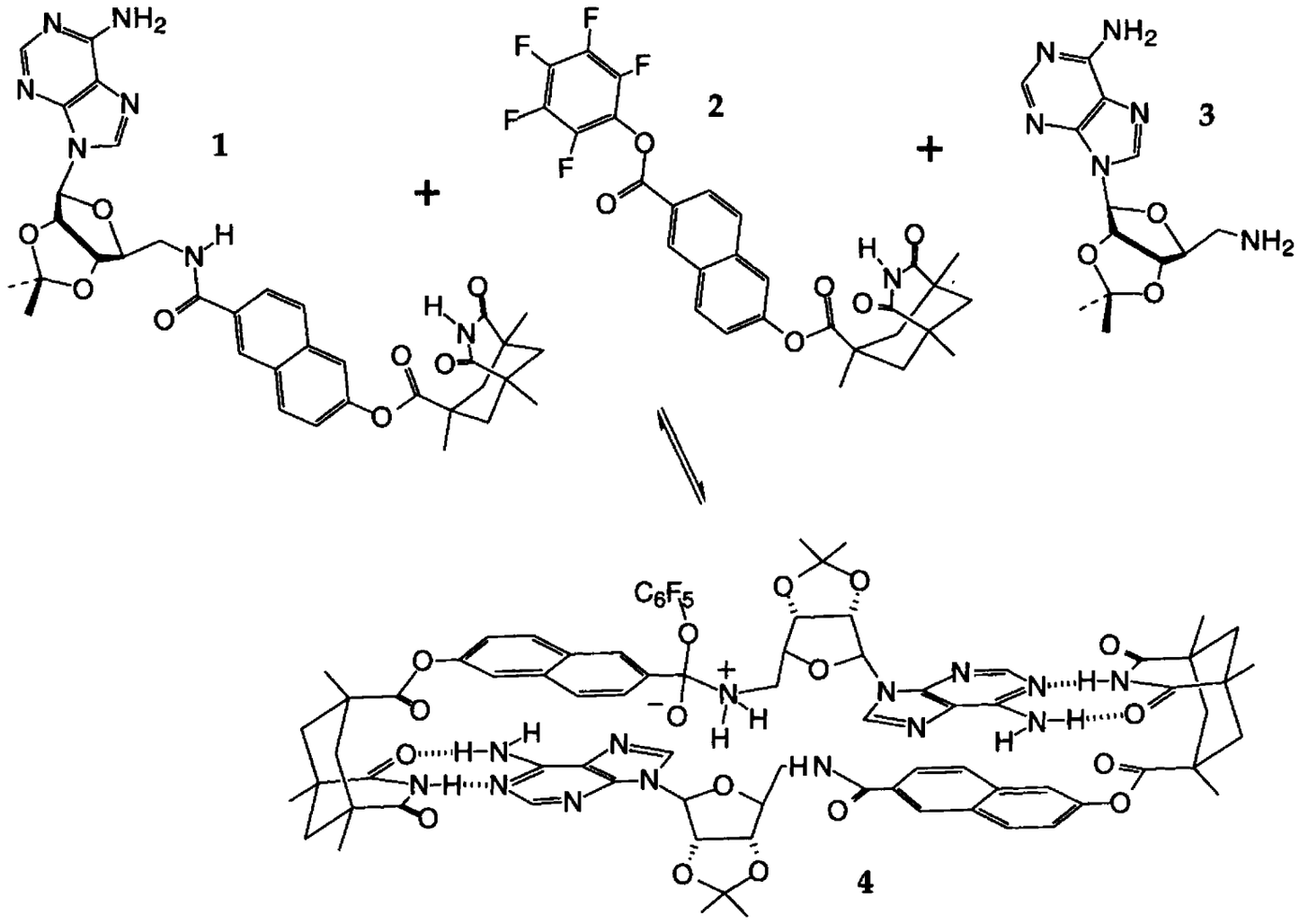




link: 有機化学美術館（http://www.org-chem.org/yuuki/replica/replica.html）

1st Generation of Self-Replicating System

- **Discovery of Synthetic Self-Replicator**



interaction by hydrogen bonding between adenine and imide

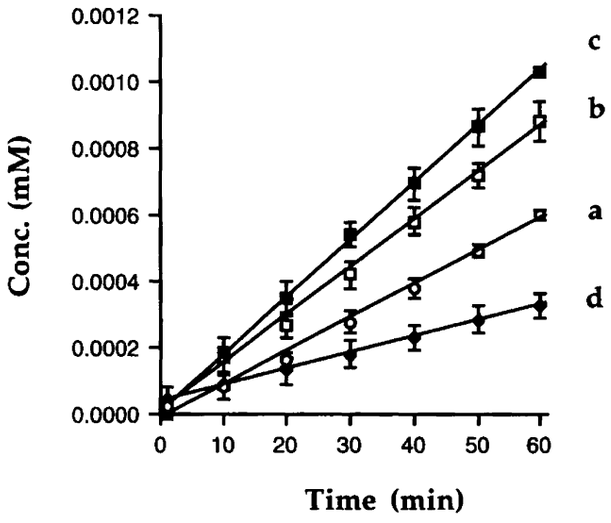


Fig. 3. Formation of **1** in $CHCl_3$ as followed by HPLC, 21 ± 1 °C; 8.2 mM initial concentrations of **2** and **3**, 1% TEA base added; (a) baseline reaction **2** + **3**; (b) baseline reaction plus 0.2 equiv. product **1**; (c) baseline reaction plus 0.5 equiv. product **1**; (d) baseline reaction plus 1.0 equiv. adenine binder **7**.

J. Rebek, Jr *J. Am. Chem. Soc.* **1990**, *112*, 1249-1250

1st Generation of Self-Replicating System

- **Simple Amide as Catalyst**

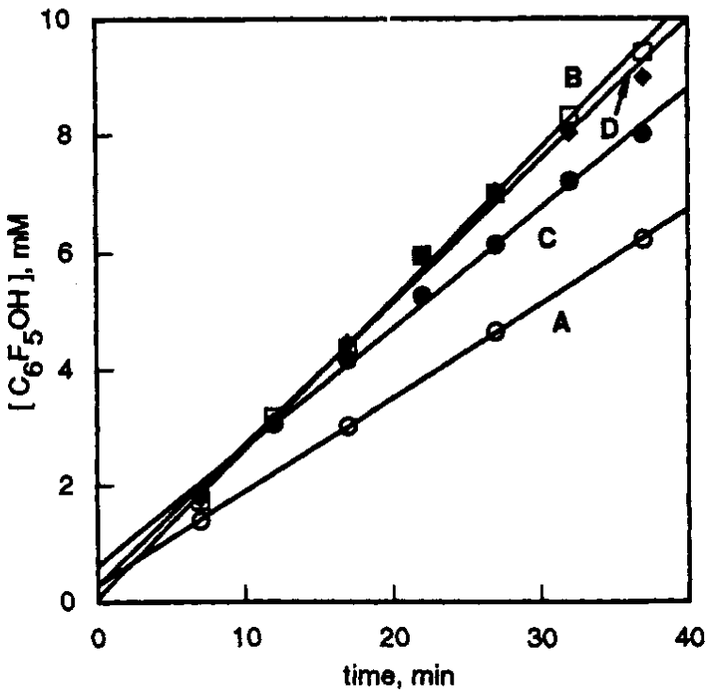


Figure 1. Initial rates of pentafluorophenol formation in the reaction of amide **1** (0.03 M) with ester **2** (0.03 M) in $CDCl_3$ in the presence of: A, no additive; B, 0.03 M amide **4**; C, 0.03 M control **9**; and D, 0.03 M acetamide. Reactions were monitored by ^{19}F NMR at 25.0 °C.

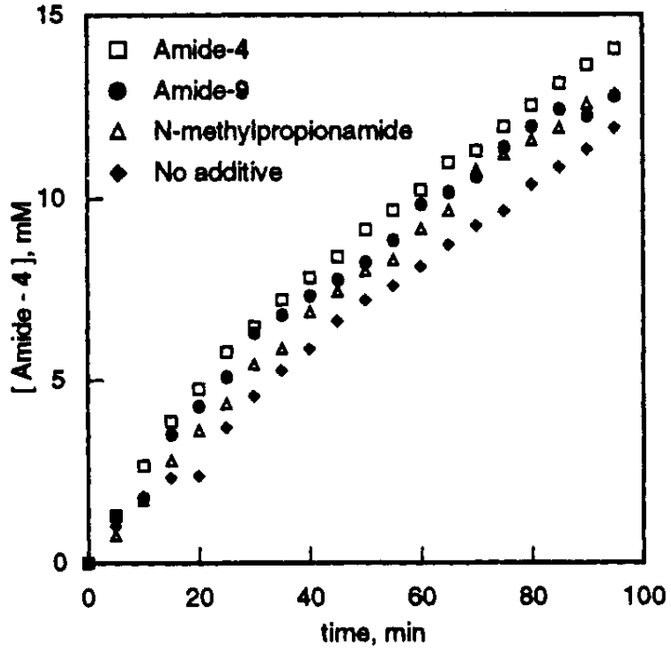
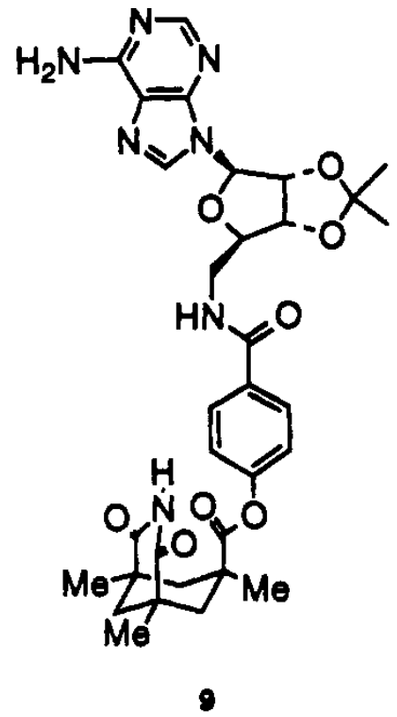


Figure 2. Time course for formation of amide **4** in the reaction between amine **1** and ester **2** in $CDCl_3$ in the presence of amide **4**, amide **9**, and *N*-methylpropionamide (all at 0.03 M). Reactions were monitored for the production of amide **4** by ^1H NMR at 25.0 °C. Error in the initial rates is estimated to be ±15%. Note that the rates in the latter part of the reaction (unexamined by Rebek[1]) are identical.



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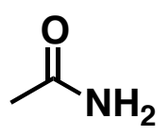
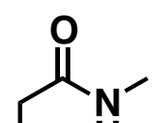


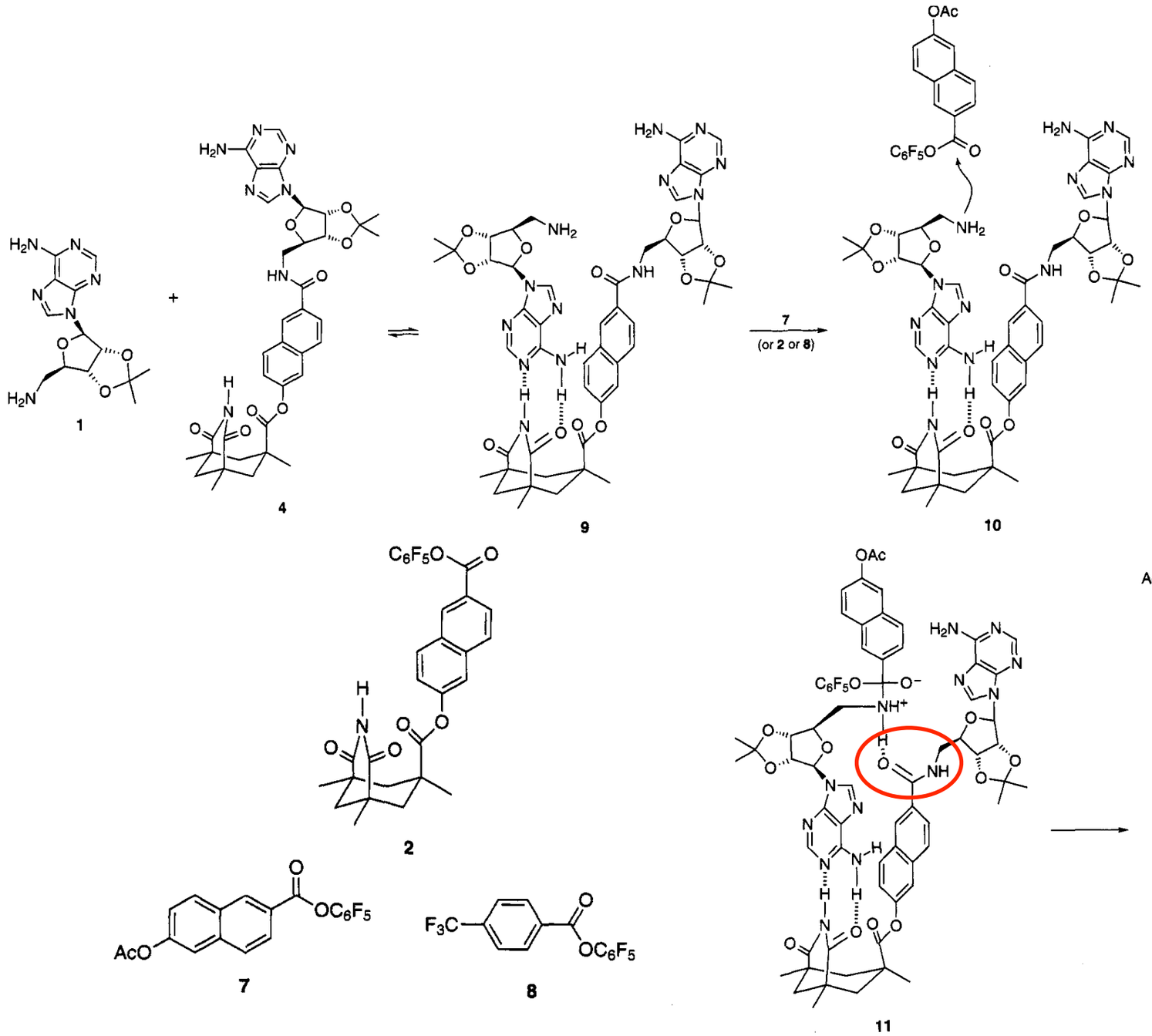


simple amide can play a role of catalyst in Rebek's self-replicating system

F. M. Menger *J. Am. Chem. Soc.* **1994**, *116*, 3613-3614; *J. Org. Chem.* **1995**, *60*, 2870-2878

1st Generation of Self-Replicating System

- **A Non-Self-Replicative Mechanism**

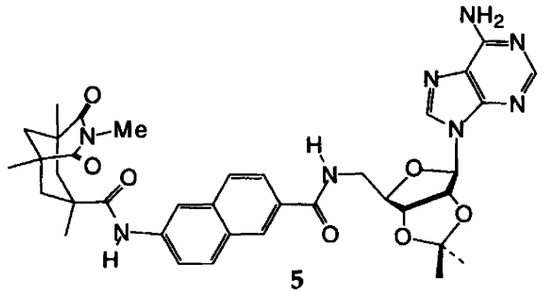


amide works as a base?

F. M. Menger *J. Org. Chem.* **1995**, *60*, 2870-2878

1st Generation of Self-Replicating System

• Control Experiment



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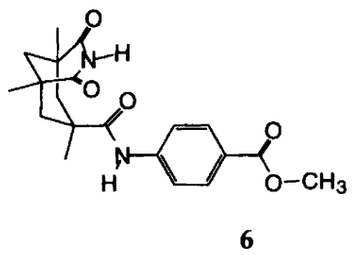

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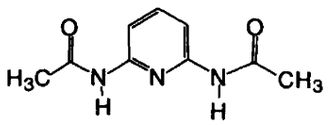

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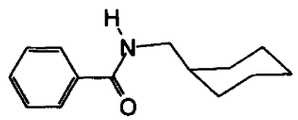

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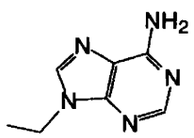

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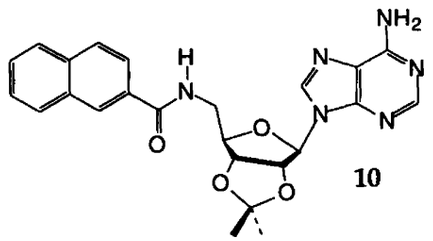

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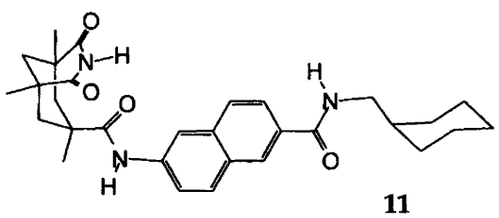

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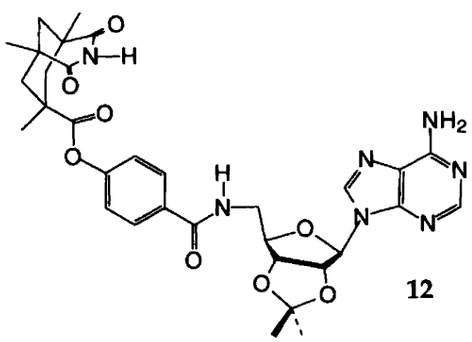
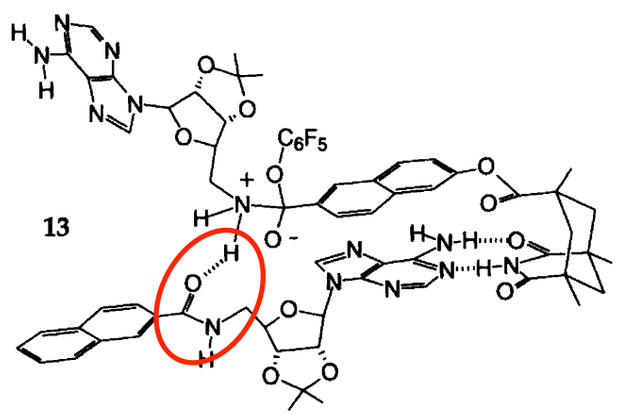


12

Table 1. Effect of various additives on the formation of **1** in $CHCl_3$ as followed by HPLC (see Ref. 21): 2.2 mM initial concentrations of **2** and **3**, 22 ± 1 °C, 1% Et_3N base added.

Entry	Additive (0.5 equiv.)	Avg. initial rate of product formation ±5%/μM min^{-1}	Percentage of baseline rate
1	—	0.54	—
2	**1**	0.81	150
3	**5**	0.55	102
4	**6**	0.56	104
5	**8**	0.52	96
6	**9**	0.55	102
7	**10**	0.50	93
8	**11**	0.56	104
9	**21**	0.63	117
10	**12**	0.57	106



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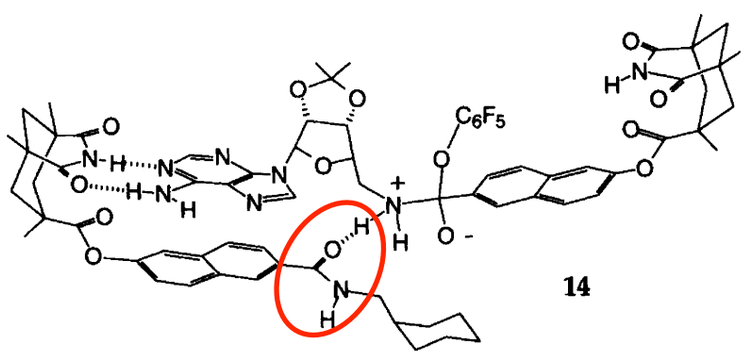


14

exclude the function of self-replicator as a simple chemical catalysis

J. Rebek, Jr *J. Am. Chem. Soc.* **1994**, *116*, 8823-8824; *J. Org. Chem.* **1995**, *60*, 7997-8001

1st Generation of Self-Replicating System

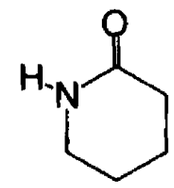
- **Exclusion of Internal Amide Catalysis**

Table 2. Generation of product **16** as a function of time, as followed by HPLC. All reactions were performed at 2.0 mM initial concentrations of reactants **3** and **15** in $CHCl_3$ with 1.0% TEA base added, 22 ± 1 °C.

Conc. of ester **15** and amine **3**/mM	Equiv. template **1**	Avg. initial rate of formation of **16**/μM min^{-1}	Relative rate
2.0	0	15.0	1
2.0	0.5	15.0	1.00
2.0	0.7	15.2	1.01

Table 3. Amide formation control experiments at 25°C as followed by NMR spectroscopy. Coupling of **17** and **18** in $CDCl_3$ with or without addition of amide **20**. Initial velocities of reaction were determined through integration of the methylene peak of the product amide **31** at 4.72 ppm relative to the methylene peak of **18** at 3.88 ppm (see Ref. 26).

Conc. of ester **17** and amine **18**/mM	Equiv. amide **20**	Avg. initial rate of formation of **19**/μM min^{-1}	Relative rate
4	0	42	1
	0.5	42	1.00
8	0	84	1
	0.5	84	1.00
16	0	168	1
	0.5	174	1.04
20	0	258	1
	0.5	282	1.09



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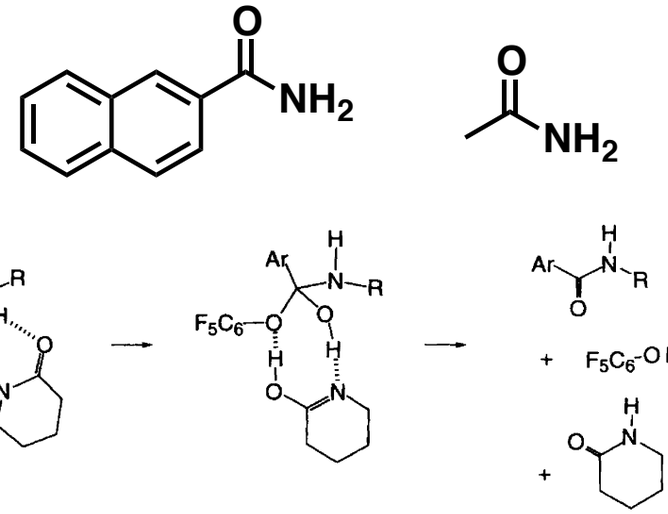


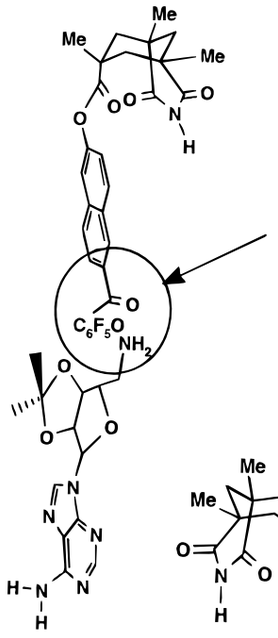
cis **amide and primary amide can catalyze the formation of amide**

BUT self-replicator is *trans* amide

J. Rebek, Jr *J. Am. Chem. Soc.* **1994**, *116*, 8823-8824; *J. Org. Chem.* **1995**, *60*, 7997-8001

1st Generation of Self-Replicating System

• Settlement of The Controversy : Kinetic Study



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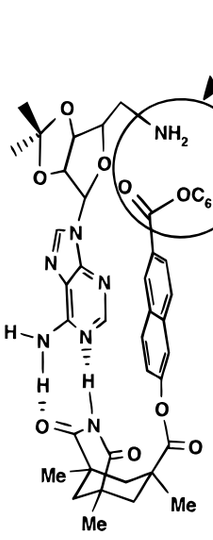

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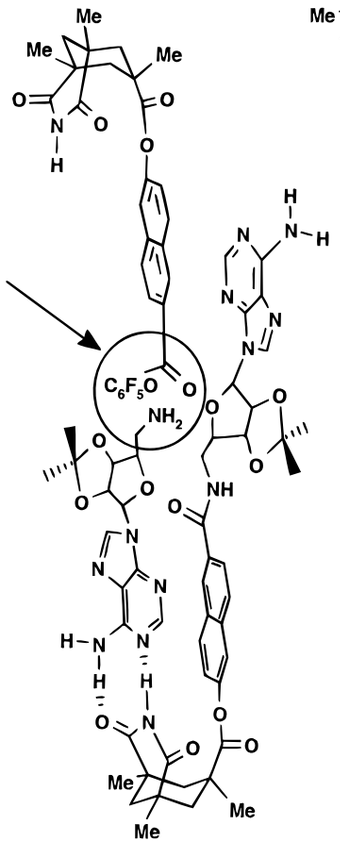
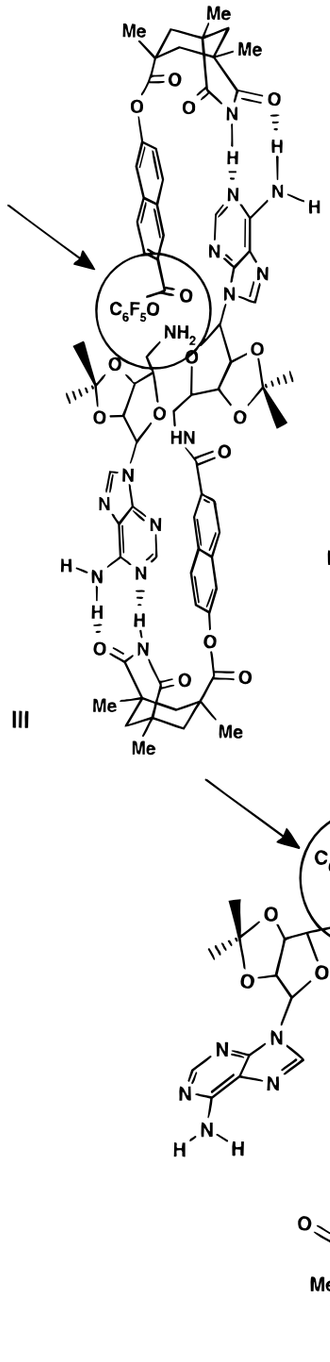


IV



III

V

dependence on the concentration of catalyst

Table 2. Calculated Initial Rates for Equimolar Amounts of **1** and **2**[a]

					contribution to initial rate (%)				
$[\mathbf{2}]_o$	$[\mathbf{1}]_o$	$[\mathbf{3}]_o$	$(dP/dt)_{calcd}$	$(dP/dt)_{obsd}$[b]	**I**	**II**	**III**	**IV**	**V**
1.67	1.67		0.10		9.5	90.5	0.0	0.0	0.0
1.67	1.67	1.67	0.14		7.0	56.4	33.7	2.5	0.4
2.2	2.2		0.17		10.1	89.9	0.0	0.0	0.0
2.2	2.2	2.2	0.24		7.2	52.5	36.8	3.0	0.5
8.2	8.2		1.5	1.4	15.8	84.2	0.0	0.0	0.0
8.2	8.2	4.1	2.2	2.0	10.7	46.6	36.9	5.0	0.8
8.2	8.2	8.2	2.5		9.6	35.8	45.9	7.5	1.2
16.5	16.5		4.4	4.1[c]	21.9	78.1	0.0	0.0	0.0
16.5	33.0		6.9	8.2	27.7	72.3	0.0	0.0	0.0
33.0	16.5		6.9	7.9	27.7	72.3	0.0	0.0	0.0
16.5	16.5	8.2	6.9	5.7[c]	13.7	38.3	38.5	8.3	1.3
16.5	16.5	11.5	7.4	5.9	12.9	33.2	42.4	10.0	1.5
16.5	16.5	16.5	7.8	6.2	12.2	28.1	45.7	12.2	1.9
30	30		10.6	12.9	29.7	70.3	0.0	0.0	0.0
30	30	15	18.2		17.4	31.1	37.2	12.5	1.9
30	30	30	20.7	16.3	15.2	22.0	42.2	17.9	2.8
50	50		22.9	47.0	38.3	61.7	0.0	0.0	0.0
50	50	25	41.3		21.2	25.3	33.8	17.2	2.6
50	50	50	48.1		18.2	17.0	37.1	24.0	3.7

[a] Concentrations in mM; rates in $M \cdot min^{-1} \times 10^5$. [b] Average rate over the first 100 min. [c] Used for parametrization.

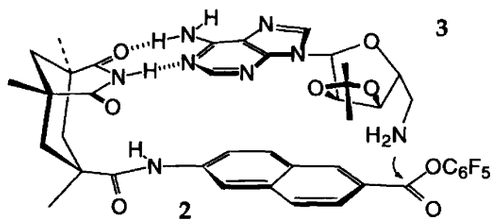
D. N. Reinhoudt *J. Am. Chem. Soc.* **1996**, *118*, 6880-6889

2nd Generation of Self-Replicating System

- **Modification of Spacer**

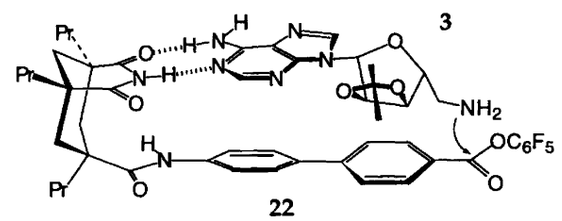
strategy : reduce the pre-associative bimolecular pathway

Hoogsteen-type



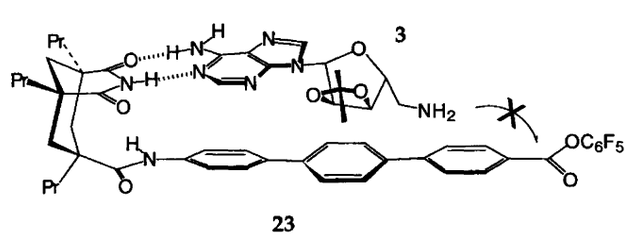
Watson-Crick-type

long



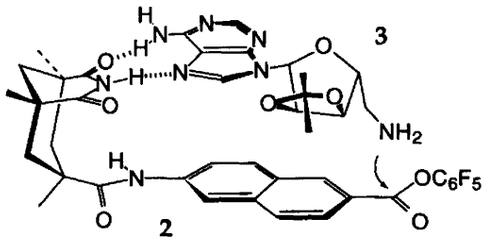
have a sigmoidal character

long



have no catalytic activity

Watson-Crick-type



short

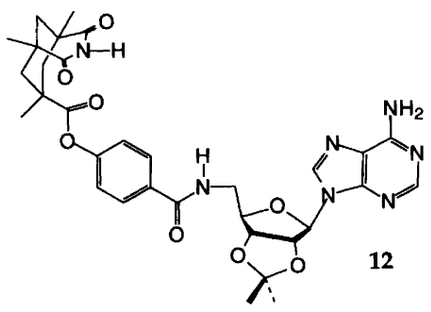
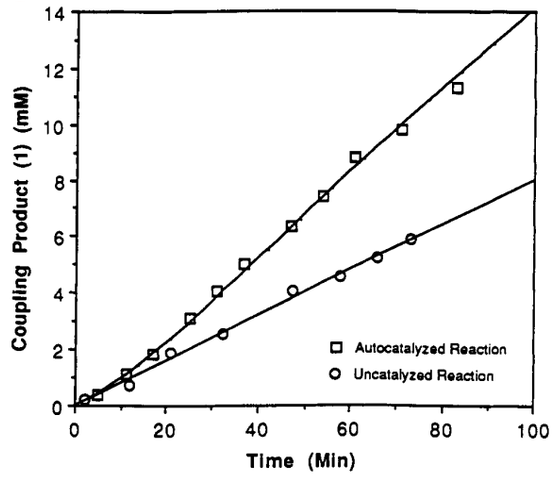


Table 1. Effect of various additives on the formation of **1** in $CHCl_3$ as followed by HPLC (see Ref. 21): 2.2 mM initial concentrations of **2** and **3**, 22 ± 1 °C, 1% Et_3N base added.

Entry	Additive (0.5 equiv.)	Avg. initial rate of product formation ±5%/μM min^{-1}	Percentage of baseline rate
10	**12**	0.57	106

have no catalytic activity



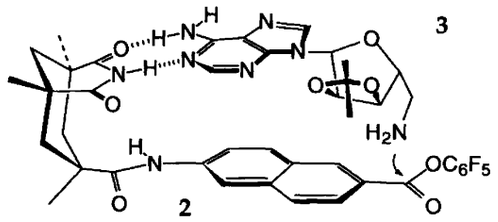
need a moderate long spacer

J. Rebek, Jr *J. Am. Chem. Soc.* **1991**, *113*, 9422-9423

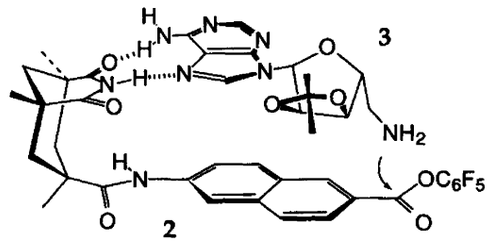
2nd Generation of Self-Replicating System

- **Modification of Backbone**

Hoogsteen-type



Watson-Crick-type

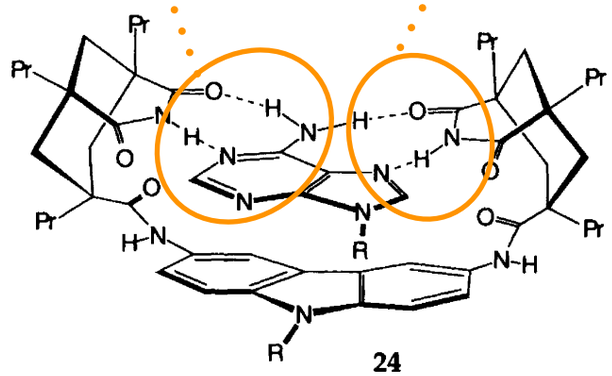


associate constant K_a = 60 M^{-1}

Hoogsteen-type

Watson-Crick-type

combine



K_a = 10^5 M^{-1}

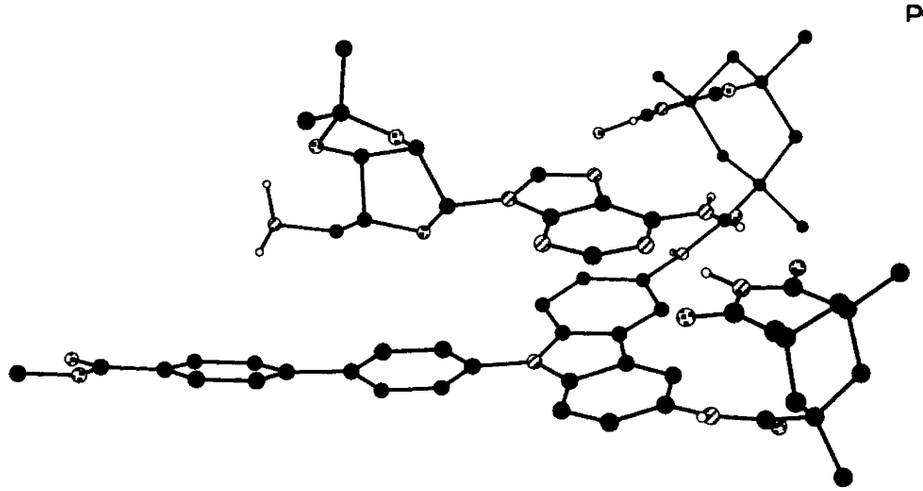
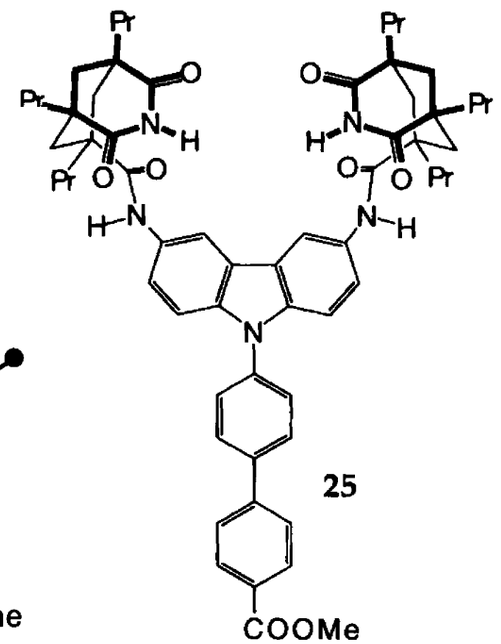


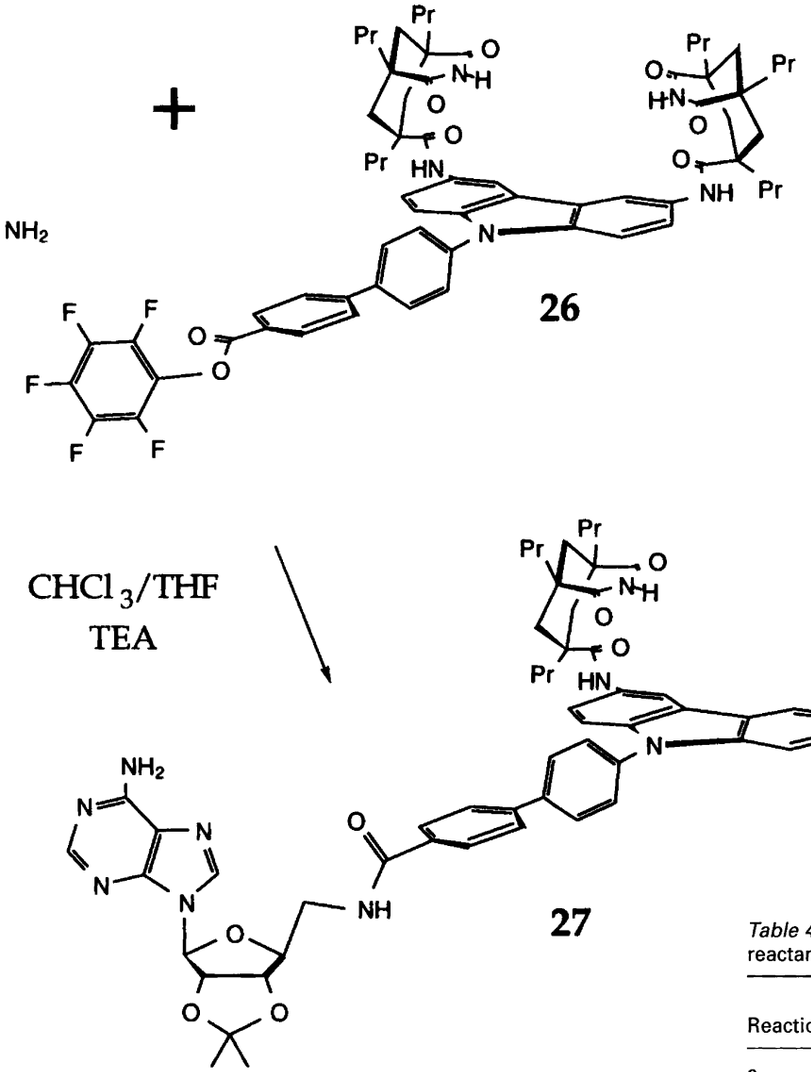
Fig. 13. Computer-generated complex[27] between the biphenylylcarbazole **25** and aminoadenosine **3**.



J. Rebek, Jr *J. Am. Chem. Soc.* **1994**, *116*, 8877-8884

2nd Generation of Self-Replicating System

- **Improvement of Autocatalytic Activity**



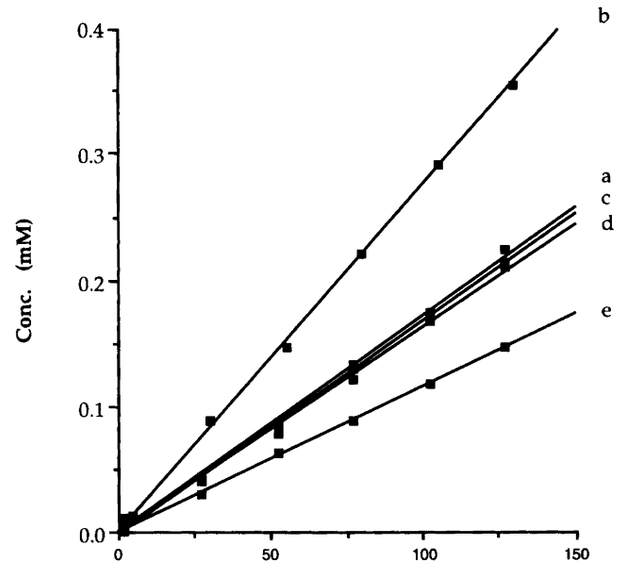


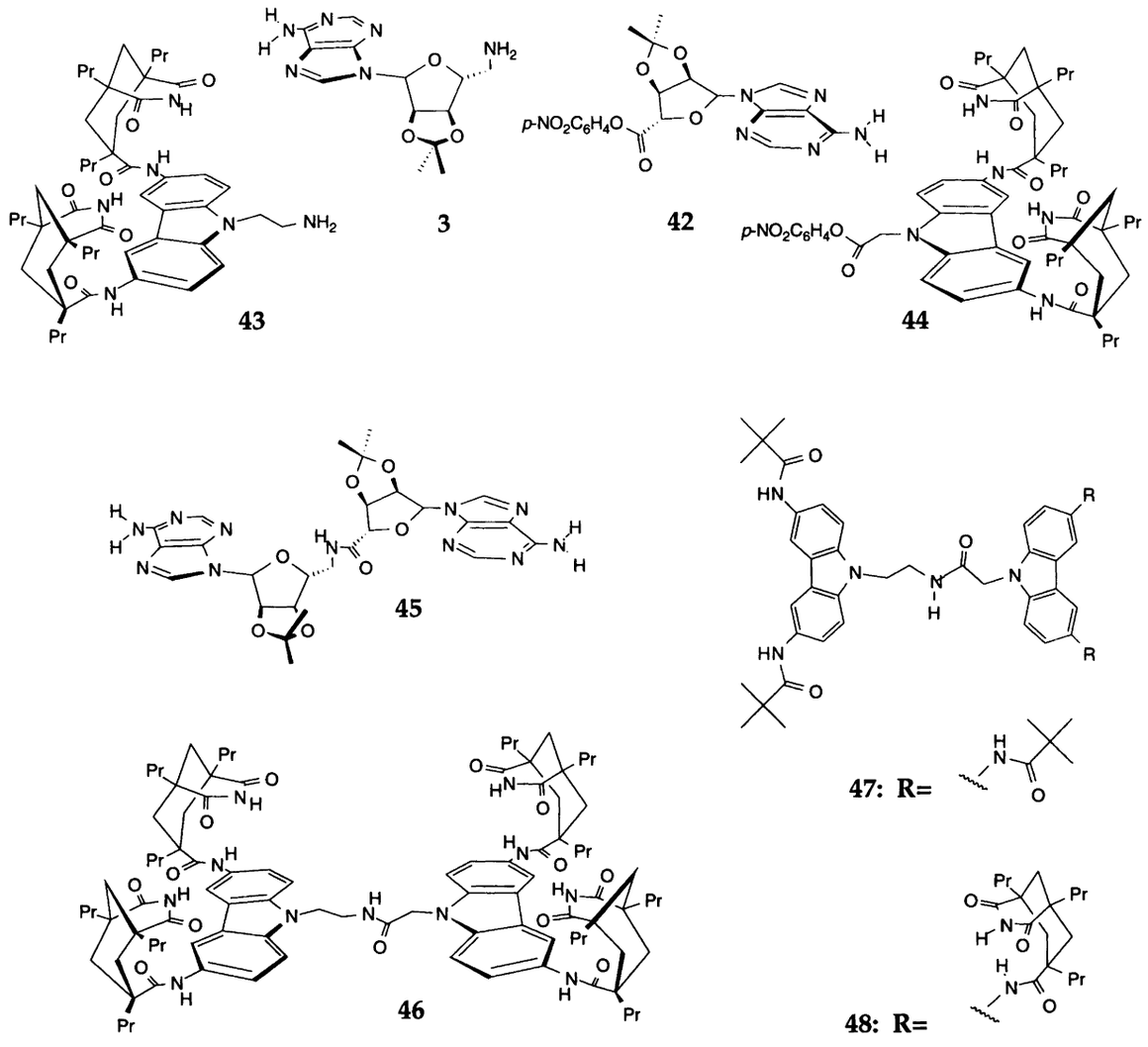
Fig. 15. Representative kinetic plots of the generation of product **27** as a function of time (initial 5% of reaction). All reactions were performed at 6.2 mM initial concentrations of reactants **3** and **26** in 13% THF–$CHCl_3$ with 1.0% TEA base added, 22 ± 1 °C. All individual slopes (reaction rates) are given in Table 1: (a) baseline reaction (**3**+**26**); (b) baseline reaction plus 0.5 equiv. product **27**; (c) baseline reaction plus 0.5 equiv. imide methyl ester **6**; (d) baseline reaction plus 1.0 equiv. amide **8**; (e) baseline reaction plus 0.5 equiv. diimide methyl ester **25**.

Table 4. Generation of product **27** as a function of time. All reactions were performed at 6.2 mM initial concentrations of reactants **3** and **26** in 13% $CHCl_3$–THF with 1.0% Et_3N base added, 22 ± 1 °C.

Reaction	Additive	Avg. initial rate of product formation/μM min^{-1}	Relative rate
a	Nothing	1.71 (6)	1.00
b	Product **27** (0.5 equiv.)	2.63 (11)	1.54 (8)
c	Imide **6** (0.5 equiv.)	1.72 (2)	1.01 (4)
d	Amide **8** (1.0 equiv.)	1.56 (8)	0.91 (6)
e	Diimide **25** (0.5 equiv.)	1.18 (10)	0.69 (6)

J. Rebek, Jr *J. Am. Chem. Soc.* **1994**, *116*, 8877-8884

Reciprocal Self-Replicating System



↑components of reciprocal self-replicating system

Table 6. Initial rates of amide formation.[50c]

Reaction[a]	Concentration/mM [45]	[46]	[9-Et-Ad.] [9]	[47]	[48]	Init. rate/nM min^{-1}[b]	Relative rate
3 + 42	—	—	—	—	—	15	1
3 + 42	0.05	—	—	—	—	16	1.1
3 + 42	—	0.05	—	—	—	150	10
3 + 42	0.05	0.05	—	—	—	42	2.8
3 + 42	—	0.05	0.5	—	—	30	2
3 + 42	—	—	0.5	—	—	15	1
3 + 42	—	—	—	0.05	—	15	1
3 + 42	—	—	—	—	0.05	11	0.7
43 + 44	—	—	—	—	—	4.3	1
43 + 44	0.05	—	—	—	—	23	5.3
43 + 44	—	0.05	—	—	—	4.3	1
43 + 44	0.05	0.05	—	—	—	13	3
43 + 44	0.05	—	0.5	—	—	15	3.5
43 + 44	—	—	0.5	—	—	4.8	1.1
42 + 43	—	—	—	—	—	53000	1
42 + 43	—	—	0.5	—	—	14000	0.3
3 + 44	—	—	—	—	—	2200	1
3 + 44	—	—	0.5	—	—	600	0.3

[a] Both components were present at 0.05 mM in $CHCl_3$ at 25 °C with 4 mM triethylamine. [b] Values are averaged from multiple independent runs. Standard deviations are ±15%.

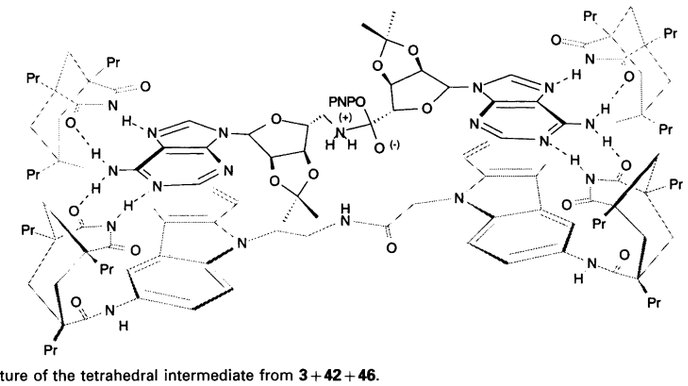


Fig. 26. Structure of the tetrahedral intermediate from **3** + **42** + **46**.

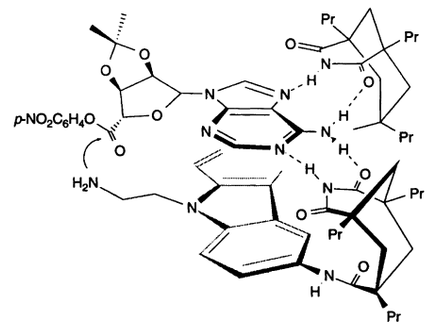


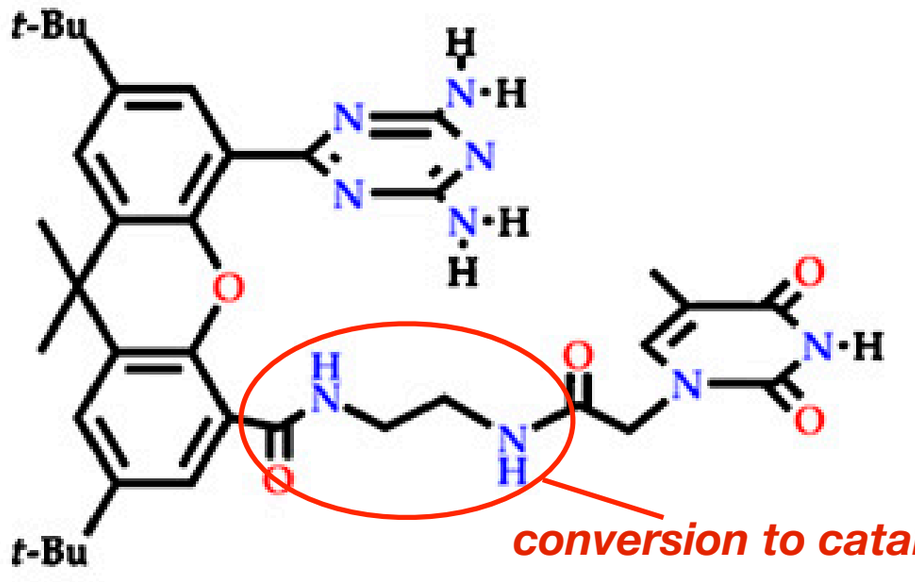
Fig. 28. Bimolecular complex proposed for the fast reaction between **42** and **43**.

J. Rebek, Jr *Tetrahedron* **1995**, *51*, 485-498

Autocatalyst as Organocatalyst

- **Strategy**

insertion of <u>a functional group known to catalyze organic transformations</u> into already known autocatalyst 1a

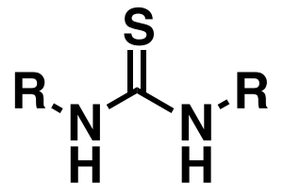


conversion to catalytic active group

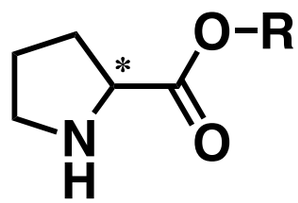
1a R = H

autocatalyst reported by Rebek and co-workers

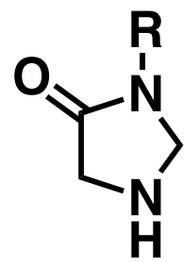
candidates of functional groups



thiourea



proline



imidazolidinone

J. Rebek, Jr *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 541-544

Autocatalyst as Organocatalyst

- **Auto-/Organocatalyst with Thiourea**

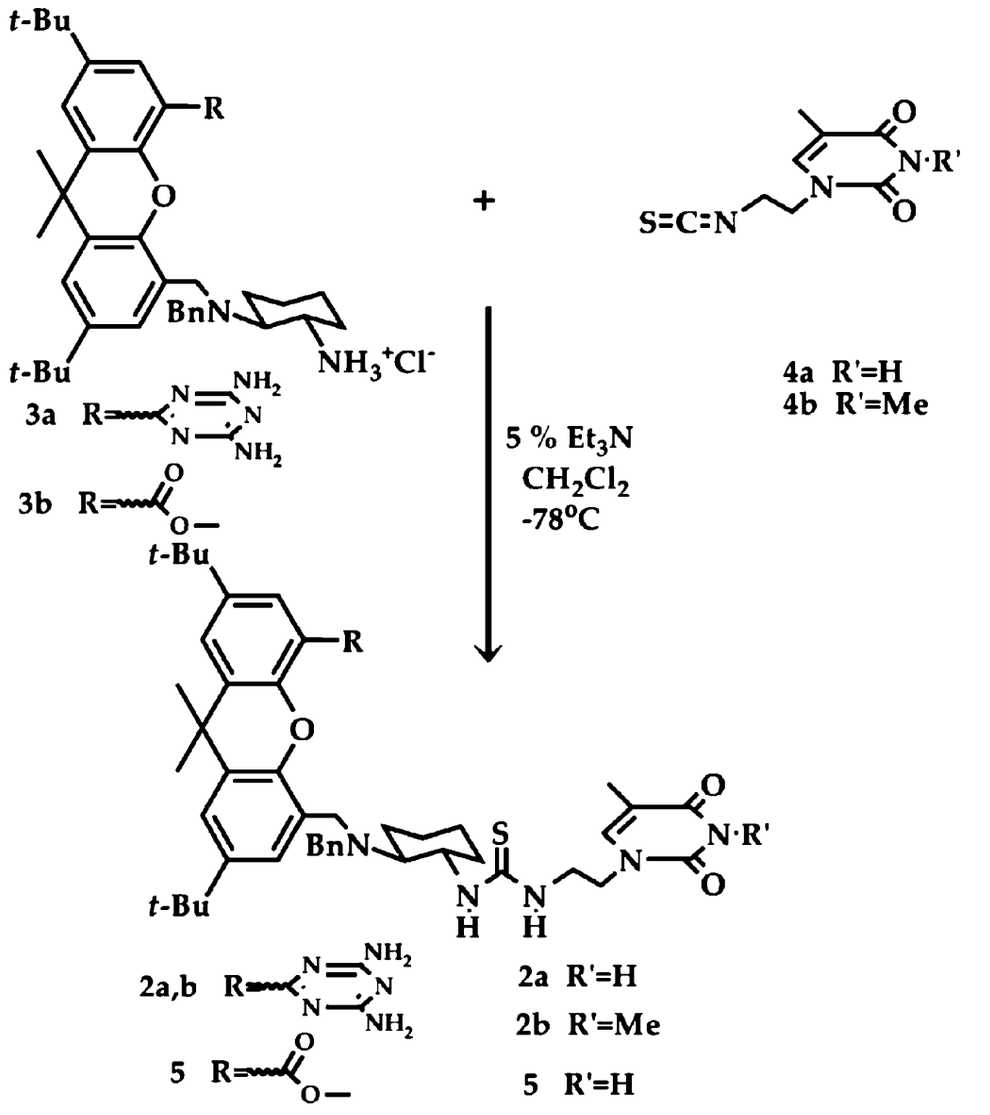


Fig. 2 The synthesis of autocatalytic and organocatalytic molecules. Both **2b** and **5** lack recognition sites and were used as controls.

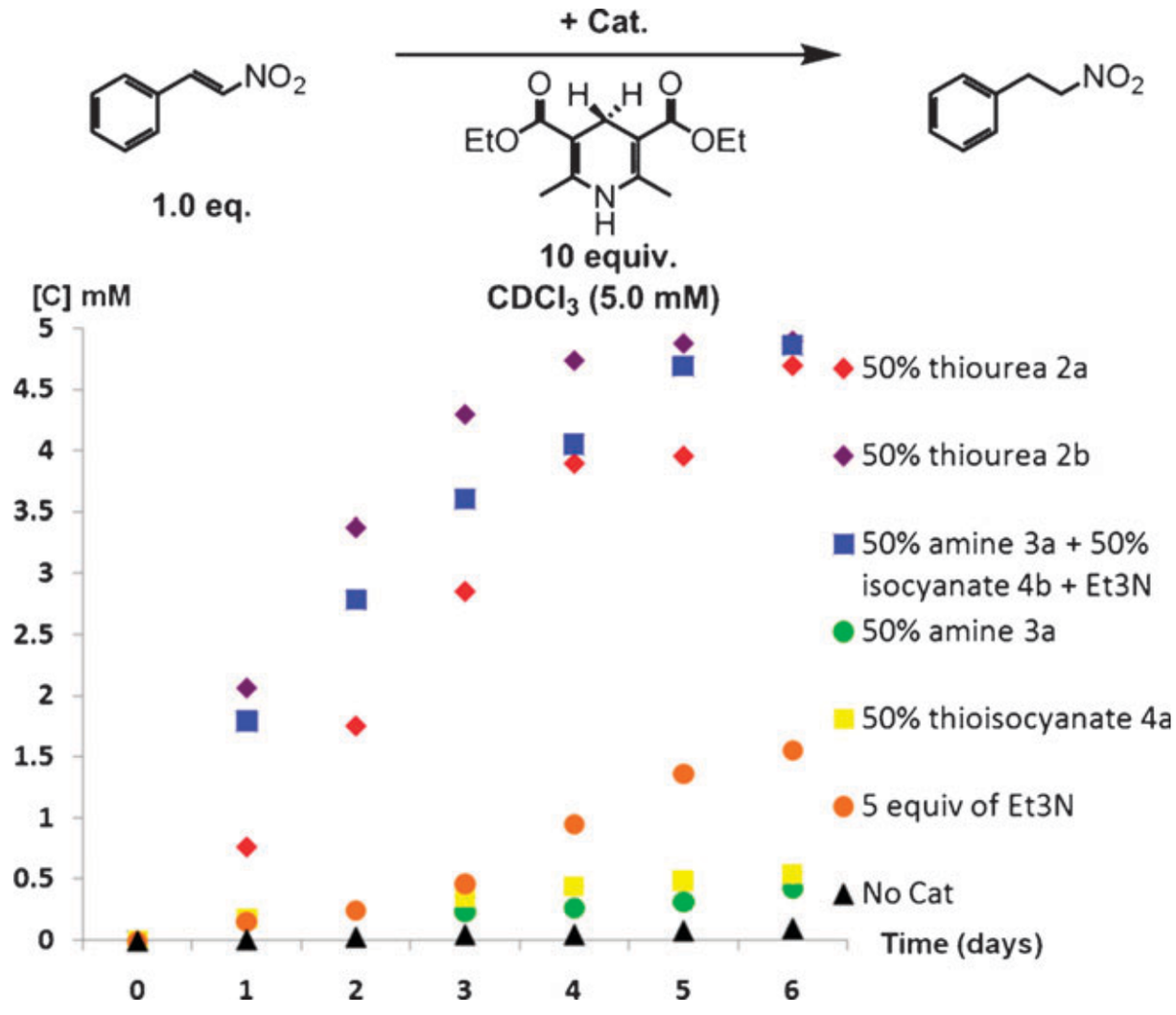
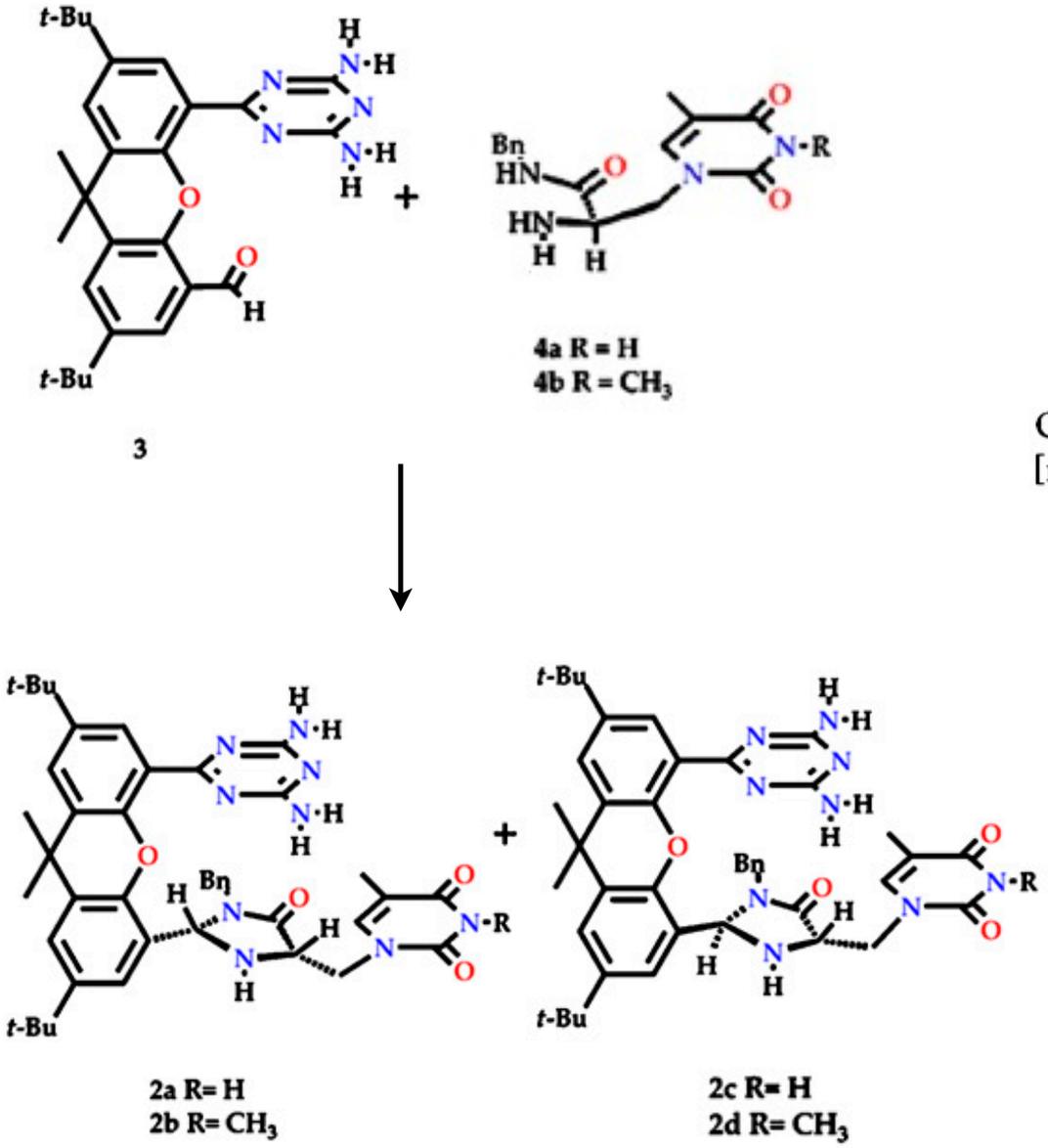


Fig. 4 The organocatalyzed reduction of a nitroolefin. The concentration of the resulting product (mM) is plotted against reaction progress (days).

J. Rebek, Jr *Chem. Comm.* **2009**, 7324-7326

Autocatalyst as Organocatalyst

- **Auto-/Organocatalyst with Imidazolidinone**



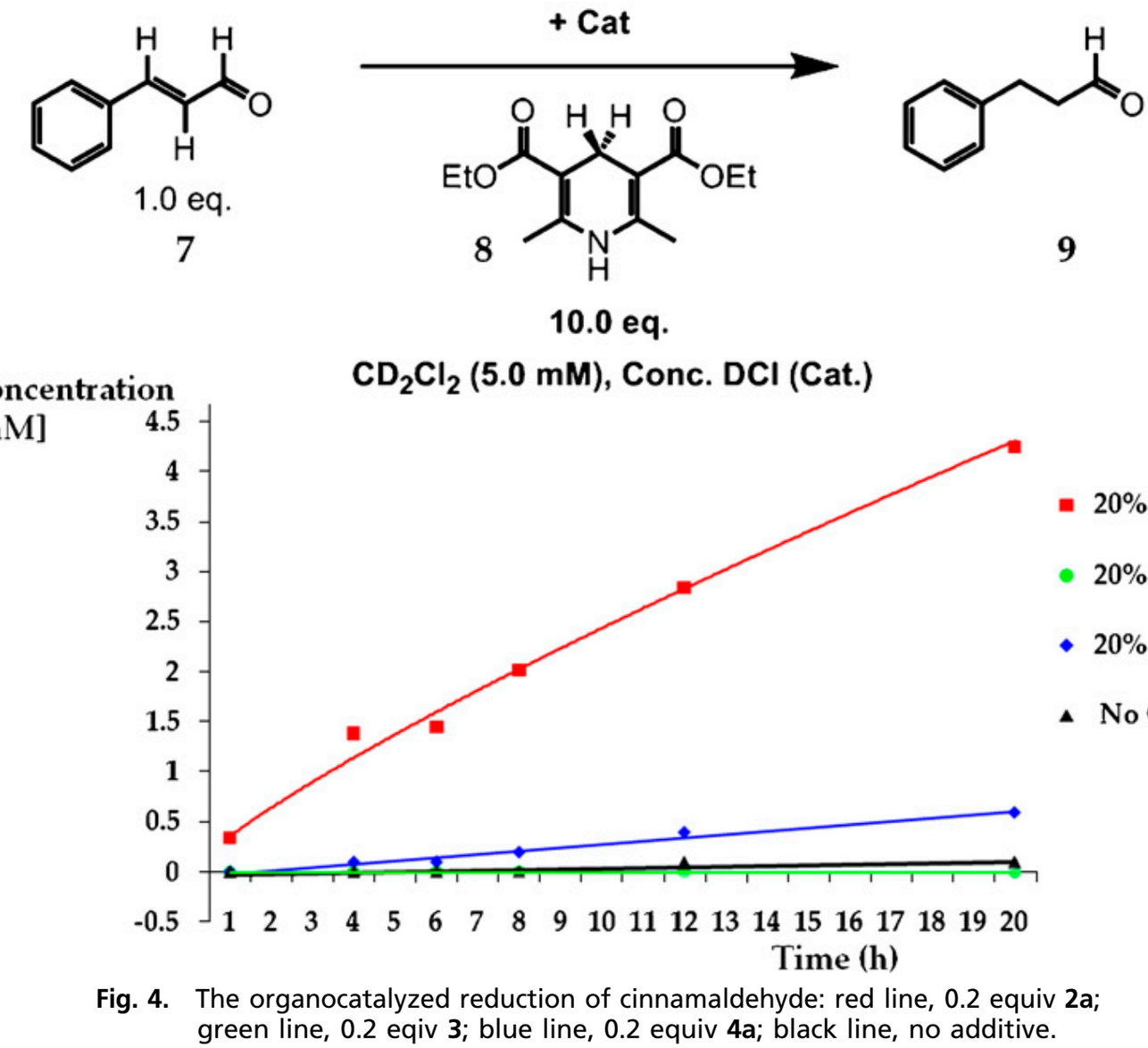


Fig. 4. The organocatalyzed reduction of cinnamaldehyde: red line, 0.2 equiv **2a**; green line, 0.2 eqiv **3**; blue line, 0.2 equiv **4a**; black line, no additive.

J. Rebek, Jr *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 541-544

IV. Biological Autocatalysis

~ Self-Replication of RNA ~

✤ **Evidence for RNA World**

What is the *RNA World* ?

RNA World is...

a self-replicating system consisting of RNA(NOT DNA/Protein), thought to exist in earlier time on the earth.

However...

There are some points to be discussed in RNA World hypothesis.

1) No evidence for forming RNA from many other nucleotide

2) Unstable structure of RNA compared to DNA

3) Never discovery of self-replicating RNA

Self-Replication of RNA

- **Discovery of *Self-Sustained* Replication of RNA**

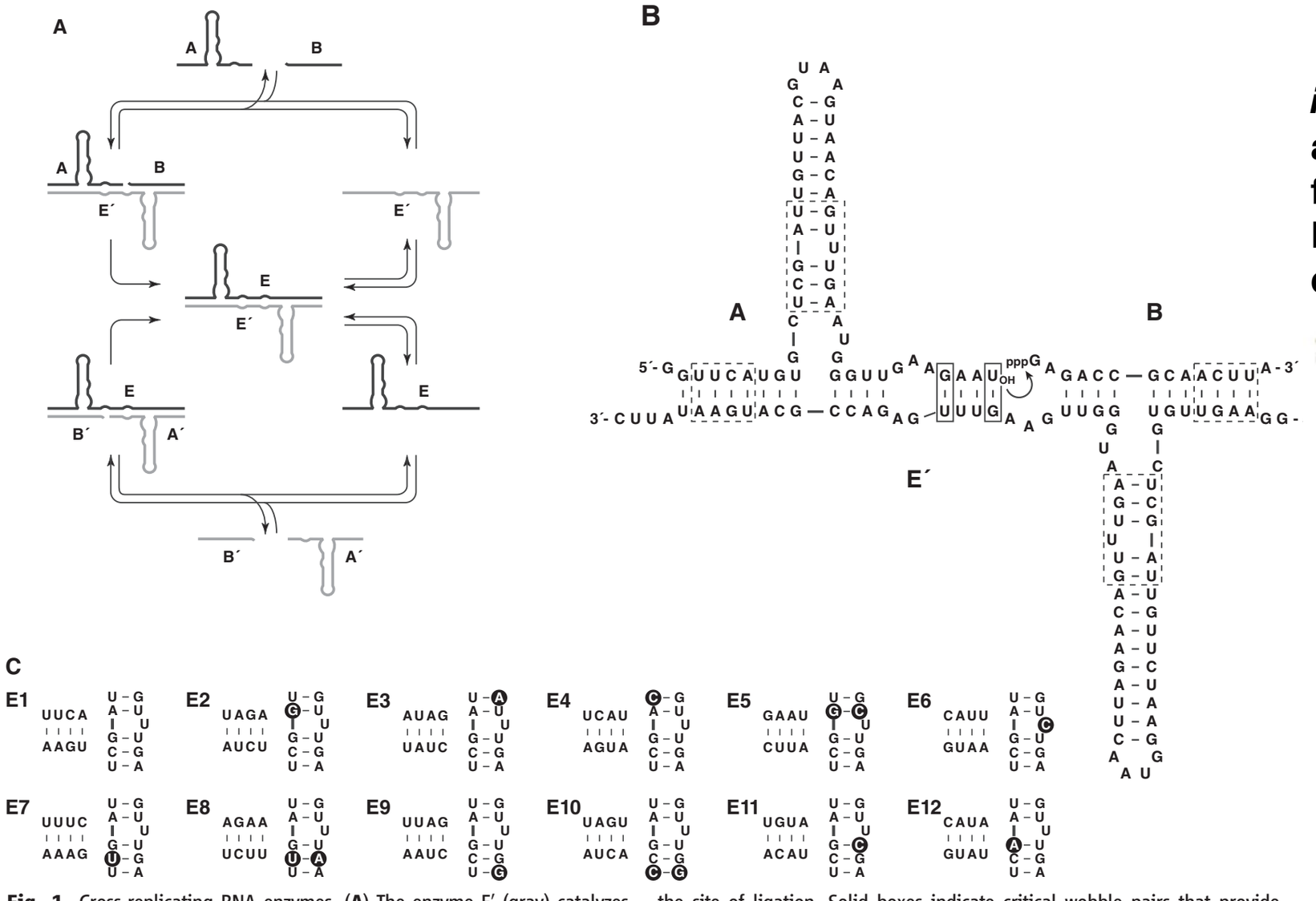
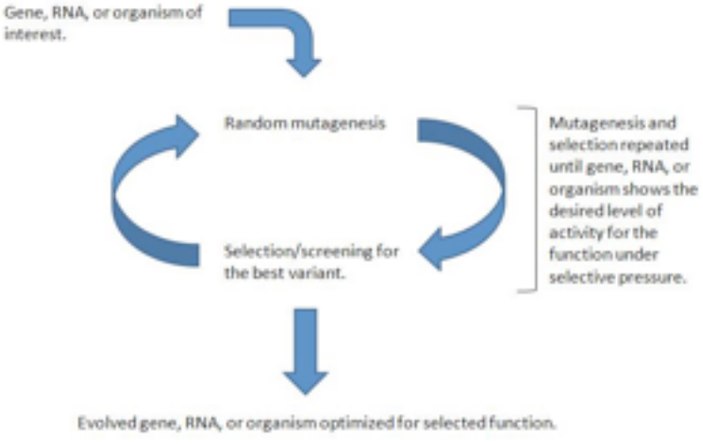


Fig. 1. Cross-replicating RNA enzymes. (**A**) The enzyme E′ (gray) catalyzes ligation of substrates A and B (black) to form the enzyme E, whereas E catalyzes ligation of A′ and B′ to form E′. The two enzymes dissociate to provide copies that can catalyze another reaction. (**B**) Sequence and secondary structure of the complex formed between the enzyme and its two substrates (E′, A, and B are shown; E, A′, and B′ are the reciprocal). The curved arrow indicates the site of ligation. Solid boxes indicate critical wobble pairs that provide enhanced catalytic activity. Dashed boxes indicate paired regions and catalytic nucleotides that were altered to construct various cross replicators. (**C**) Variable portion of 12 different E enzymes. The corresponding E′ enzymes have a complementary sequence in the paired region and the same sequence of catalytic nucleotides (alterations relative to the E1 enzyme are highlighted).

***in vitro* evolution :**
a technique used to explore the functional capabilities of RNA and DNA in a rapid, systematic, and directed fashion.



G. F. Joyce *Science* **2009**, *323*, 1229-1232

Self-Replication of RNA

- ***Self-Sustained*** **amplification of RNA**

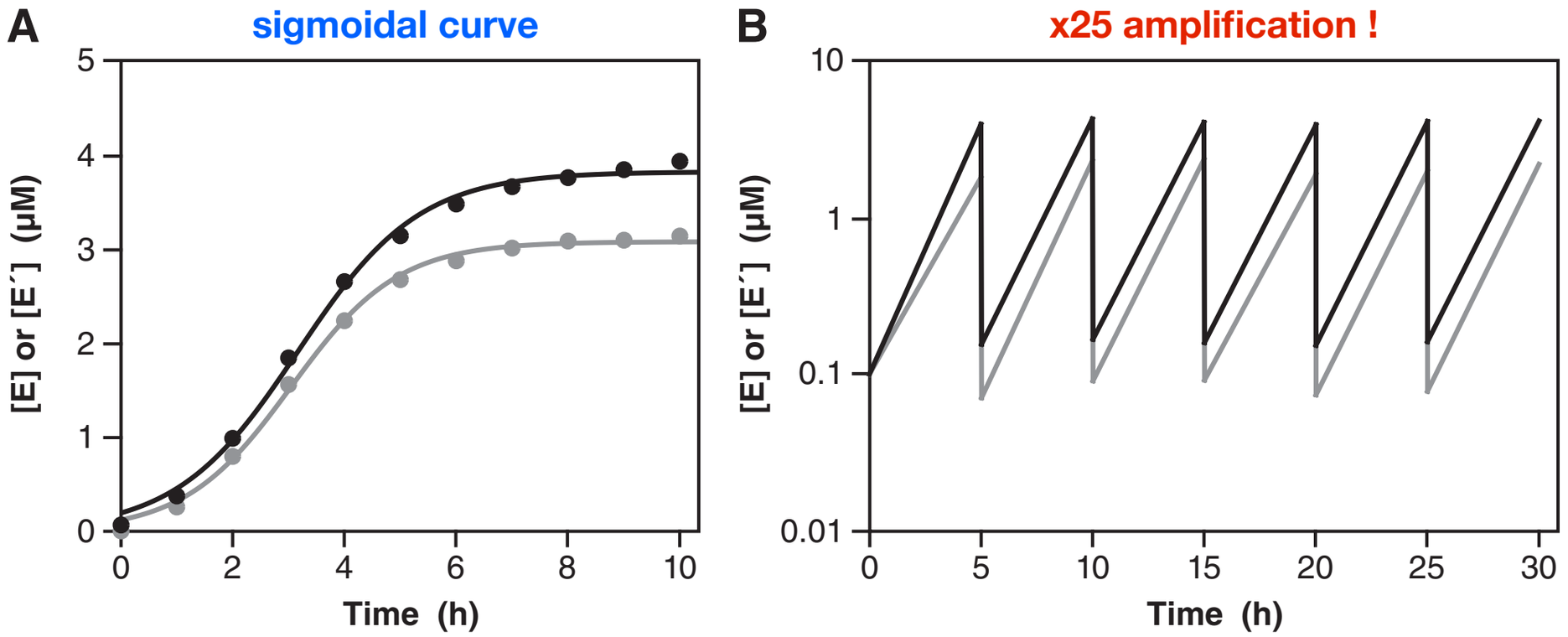


Fig. 2. Self-sustained amplification of cross-replicating RNA enzymes. (**A**) The yield of both E (black curve) and E′ (gray curve) increased exponentially before leveling off as the supply of substrates became exhausted. (**B**) Amplification was sustained by performance of a serial transfer experiment, allowing approximately 25-fold amplification before transferring 4% of the mixture to a new reaction vessel that contained a fresh supply of substrates. The concentrations of E and E′ were measured at the end of each incubation.

G. F. Joyce *Science* **2009**, *323*, 1229-1232

V. Summary

Summary of Today's Topics

- **Asymmetric Autocatalysis → Homochirality**
- **Organic Autocatalysis → Synthetic Biology**
- **Biological Autocatalysis → RNA World Hypothesis**

} ***"bottom up" approach to life***

- ***Can We Utilize Autocatalytic Reactions to Accomplish More Efficient Organic Synthesis ?***